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[Ledger Number of Payment in advance] 029595

[Charge] 21,000

[List of Documents filed]

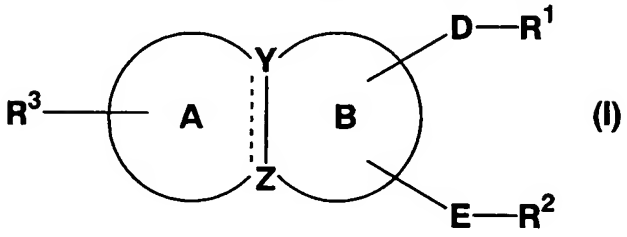
[Name of Document] Claims 1

[Name of Document] Specification 1

[Name of Document] Abstract 1

[Name of Document] Claims

[Claim 1] A compound of formula (I)



[wherein

R^1 and R^2 are each independently, an acidic group which may be protected,

D and E are each independently, a bond or a spacer consisting of 1-8 of atom in the main chain,

R^3 is a substituent,

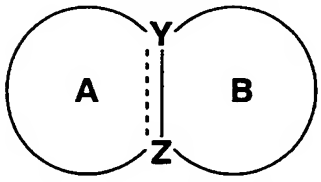
ring A is a cyclic group which may have further substituent(s),

ring B is a cyclic group which may have further substituent(s),

Y and Z are each independently, a carbon atom or a nitrogen atom, and

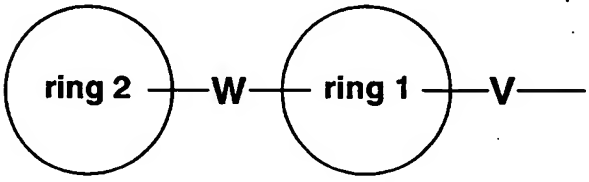
--------- is a single bond or a double bond (provided that Y and/or Z is/are nitrogen atom(s), the bond is a single bond.).], a pharmaceutically acceptable salt thereof, a solvate thereof or a prodrug thereof.

[Claim 2] The compound according to claim 1, wherein



is 3,4-dihydro-2H-1,4-benzoxazine, 3,4-dihydro-2H-1,4-benzothiazine, 1,2,3,4-tetrahydroquinoxaline, 1,2,3,4-tetrahydroquinoline, 1,2-dihydroquinoline, 4H-1,4-benzoxazine, 4H-1,4-benzothiazine, quinoline, isoquinoline, quinoxaline, 1,2,3,4-tetrahydroisoquinoline, cinnoline, phthalazine, 4(1H)-quinolinone, 3,4-dihydro-2(1H)-quinolinone, or 2(1H)-quinolinone ring.

[Claim 3] The compound according to claim 1, wherein R^3 is



[wherein

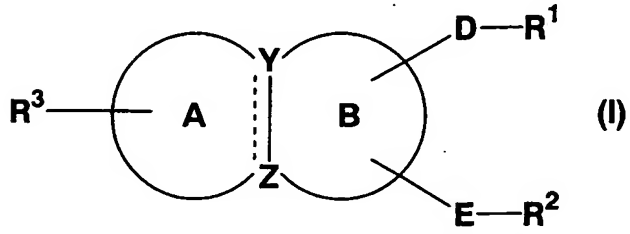
ring 1 is a cyclic group which may have substituent(s),

V is a bond or a spacer having 1-8 of atom in the main chain,

ring 2 is a cyclic group which may have substituent(s), and

W is a bond or a spacer having 1-8 of atom in the main chain].

[Claim 4] A cysLT$_2$ receptor antagonistic agent comprising the compound of formula (I)

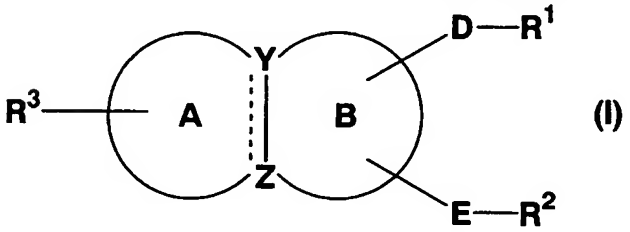


[wherein, all symbols have the same meanings as in claim 1], a pharmaceutically acceptable salt thereof, a solvate thereof or a prodrug thereof.

[Claim 5] The agent according to claim 4, which is an agent for the prevention and/or treatment of a respiratory disease.

[Claim 6] The agent according to claim 5, which is an agent for the prevention of asthma.

[Claim 7] A pharmaceutical composition comprising the compound of formula (I)

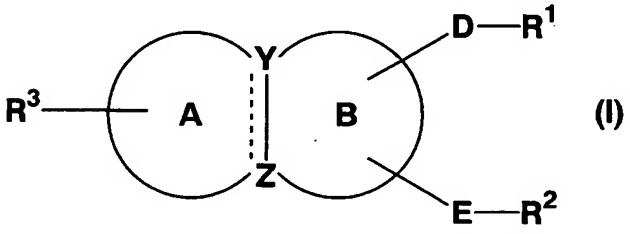


[wherein, all symbols have the same meanings as in claim 1], a pharmaceutically acceptable salt thereof, a solvate thereof or a prodrug thereof.

[Claim 8] The pharmaceutical composition according to claim 7, which is a cysLT$_2$ receptor antagonistic agent.

[Claim 9] The pharmaceutical composition according to claim 8, which is combined with one or more member(s) selected from a cysLT$_1$ receptor antagonist, a steroidal agent and a sympathomimetic agent.

[Claim 10] A method for the antagonizing cycLT$_2$ receptor, characterized by administering to a mammal an effective amount of the compound of formula (I),

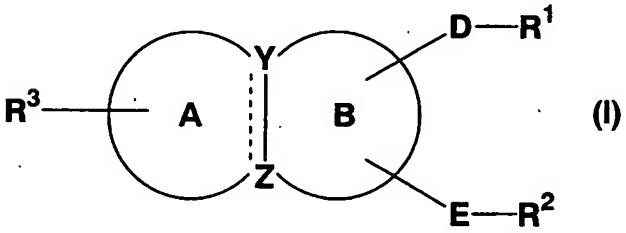


[wherein, all symbols have the same meanings as in claim 1], a pharmaceutically acceptable salt

thereof, a solvate thereof or a prodrug thereof according to claim 1.

[Claim 11] The method according to claim 10, which is the method for the prevention and/or treatment of a respiratory disease.

[Claim 12] Use of the compound of formula (I)



[wherein, all symbols have the same meanings as in claim 1], a pharmaceutically acceptable salt thereof, a solvate thereof or a prodrug thereof for the manufacture of an antagonistic agent of $cysLT_2$ receptor.

[Claim 13] The use according to claim 12, which is the use for the manufacture of an agent for the prevention and/or treatment of a respiratory disease.

[Claim 14] A pharmaceutical composition comprising the compound having $cysLT_2$ receptor antagonistic activity.

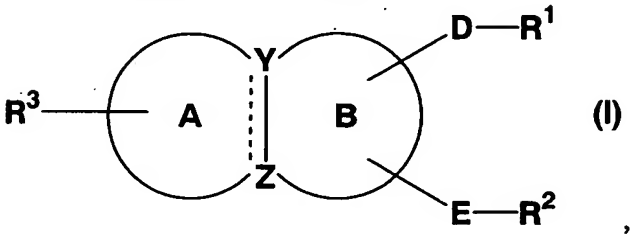
[Name of Document] Specification

[Title of the Invention] A fused compound and its use

[Technical Field]

The present invention relates to

(1) a compound of formula (I)



[wherein all symbols have the same meanings as defined below], and

(2) a cysLT$_2$ receptor antagonistic agent comprising the compound of formula (I).

[Background Art]

Bronchial asthma is a pathological symptom, in which airway is contracted by airway contraction and inflammation, causing paroxysmal cough, stridor, and breathing difficulty. The drugs for it include steroidal agents for inhalation, which have a strong antiinflammatory effect, β stimulants and theophyllines which are bronchodilating agents, antiallergic agents which inhibit the effect of mediators, etc.

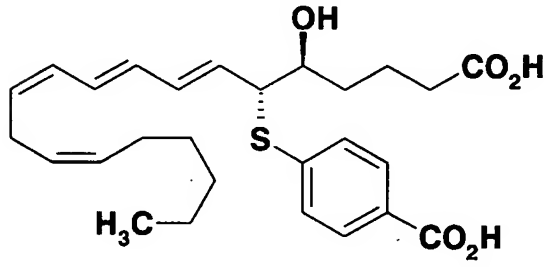
It is known that various chemical mediators are involved in bronchial asthma, among which cysteinyl leukotrienes (cysLTs) are known to have approximately 1000 times stronger contractile effect on airway as compared to histamine. Moreover, cysLTs promote induction of airway inflammation, typically inflammation cell invasion, airway hypersensitivity and mucus secretion in airway, and they are deeply involved in basic pathology of bronchial asthma.

CysLTs are a physiological active substance in a live body, which is a metabolic product from arachidonic acid by 5-lipoxygenase. CysLTs have at least two types of receptors, and cysLT$_1$ receptor and cysLT$_2$ receptor have been cloned so far (Nature, 399, 789-793, 1999, J. Biol., Chem., 275, 30531-30536, 2000). CysLT$_1$ receptor is mainly expressed in airway smooth muscle and it is deeply concerned with the development of bronchial asthma (Am. J. Respir. Crit. Care Med., 163, 226-233, 2001). Those leukotriene (LT) receptor antagonists which are now placed on the market, e.g. pranlukast hydrate, montelukast sodium and zafirlukast, and are selective cysLT$_1$ receptor antagonist (Nature, 399, 789-793, 1999), are useful agents for the treatment of bronchial asthma, which improves various kinds of symptoms and respiratory functions. However, it is known the LT receptor antagonists placed on the market are more effective for mild or moderate symptoms than for severe symptoms. It is also known that there exist some non-responders with mild or moderate symptoms on whom the pharmaceutical agent does not have effect.

On the other hand, it is reported that the ligands for the newly cloned $cysLT_2$ receptor are LTC_4, LTD_4 and LTE_4, and $cysLT_2$ receptor is expressed in the bronchial smooth muscle like $CysLT_1$ receptor (J. Biol. Chem., 275, 30531-30536, 2000, Am. J. Respir. Crit. Care Med., 164, 2098-2101, 2001). However, the functions and roles of $cysLT_2$ receptor in the pathological conditions have not been elucidated yet.

Therefore, provided that $cysLT_2$ receptor, as well as $cysLT_1$ receptor, is concerned with contraction of bronchial smooth muscle, airway inflammation, reactive airway disease and mucus secretion in airway, by antagonizing $cysLT_2$ receptor, it is conceivably possible to produce an agent for respiratory diseases which is more useful than existing LT receptor antagonists. For example, it is expected that such agent shows an efficacy on more severe bronchial asthma patients and non-responders of existing LT receptor antagonists.

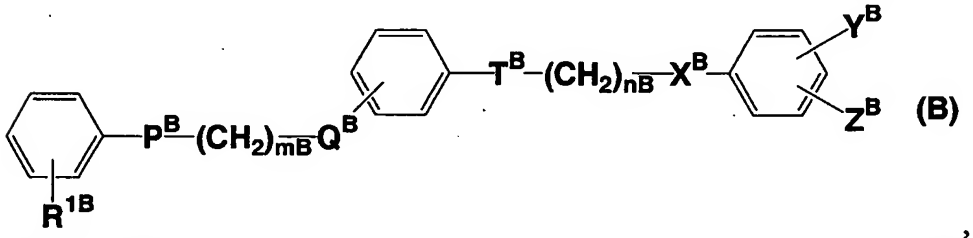
In nonpatent literature 1, it is disclosed that a compound of formula (A)



(A)

antagonizes both $cysLT_1$ and $cysLT_2$.

And in patent literature 1, it is disclosed that a benzoic acid derivative of formula (B)



(B)

wherein, R^{1B} is hydrogen, alkyl having up to 6 carbons, or substituted phenyl; P^B and Q^B is each oxygen, sulfur or a bond; X^B is oxygen, sulfur or -CONH-; T^B is ethylene, oxygen, sulfur or a bond; Y^B is -COOH, $-NHSO_2R^{3B}$ or $CONHSO_2R^{3B}$; Z^B is -COOH, COR^{4B}, $-CO(CH_2)_{pB}CO_2H$, $-O(CH_2)_{pB}CO_2H$, $-S(CH_2)_{pB}CO_2H$, NO_2, $-CONHW^BCO_2H$ or NHW^BCO_2H; mB is an integer from 0 to 6; and nB is an integer from 0 to 4

shows leukotriene antagonistic action, that is effective for the treatment of respiratory diseases, and that it antagonizes both $cysLT_1$ receptor and $cysLT_2$ receptors.

Also, in nonpatent literature 2, it is described that DUO-LT, which is a compound whose clinical target is ischemic diseases and inflammatory diseases, antagonizes both $cysLT_1$ and $cysLT_2$ receptors.

[patent literature 1] JP9-169712

[nonpatent literature 1] Molecular Pharmacology (United States), 2000, 58, p.1601-1608

[nonpatent literature 2] program of the 98th American Thoracic Society, 2002, D38, F4

[Disclosure of the Invention]

[Problems to be solved by the Invention]

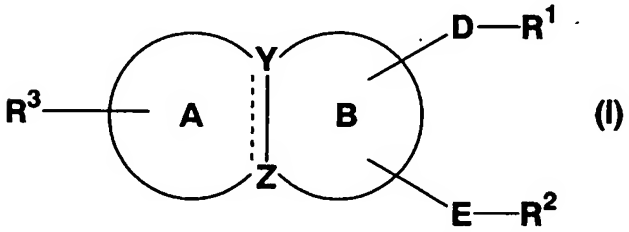
As described hereinbefore, those LT receptor antagonists which are placed on the market are known to act on mild and moderate symptoms of bronchial asthma and it is also known that there exist some non-responders among patients with mild and moderate symptoms, to whom the agents are not effective. Therefore, those agents for respiratory diseases showing higher efficacy than the existing agents have been hoped for.

[Means to solve the Problems]

The present inventors have energetically investigated to solve the above-mentioned problems, and have found out that the compound of formula (I) which antagonizes $cysLT_2$ receptor is useful as an agent for respiratory diseases to complete the present invention.

That is, the present invention relates to

(1) a compound of formula (I)



[wherein R^1 and R^2 are each independently, an acidic group which may be protected, D and E are each independently, a bond or a spacer consisting of 1-8 of atom in the main chain, R^3 is a substituent, ring A is a cyclic group which may have more substituent(s), ring B is a cyclic group which may have more substituent(s), Y and Z are each independently, a carbon atom or a nitrogen atom, and

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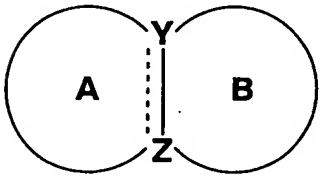
is a single bond or a double bond (provided that Y and/or Z is/are nitrogen atom(s), the bond is a single bond.).], a pharmaceutically acceptable salt thereof, a solvate thereof or a prodrug thereof,

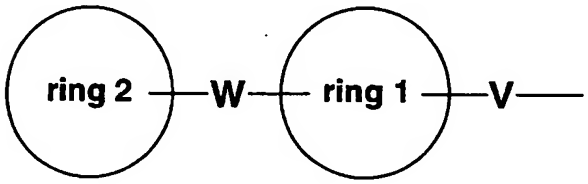
(2) the compound described in the above (1), wherein



is 3,4-dihydro-2H-1,4-benzoxazine, 3,4-dihydro-2H-1,4-benzothiazine,

1,2,3,4-tetrahydroquinoxaline, 1,2,3,4-tetrahydroquinoline, 1,2-dihydroquinoline, 4H-1,4-benzoxazine, 4H-1,4-benzothiazine, quinoline, isoquinoline, quinoxaline, 1,2,3,4-tetrahydroisoquinoline, cinnoline, phthalazine, 4(1H)-quinolinone, 3,4-dihydro-2(1H)-quinolinone, or 2(1H)-quinolinone ring,

(3) the compound described in the above (1), wherein R^3 is



[wherein

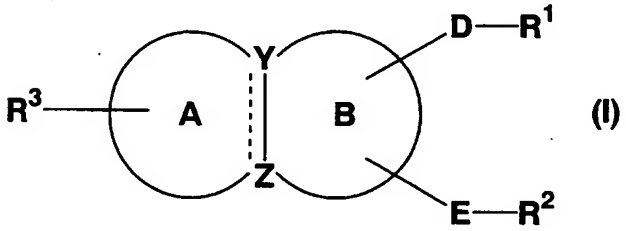
ring 1 is a cyclic group which may have substituent(s),

V is a bond or a spacer having 1-8 of atom in the main chain,

ring 2 is a cyclic group which may have substituent(s), and

W is a bond or a spacer having 1-8 of atom in the main chain],

(4) a cysLT$_2$ receptor antagonistic agent comprising the compound of formula (I)

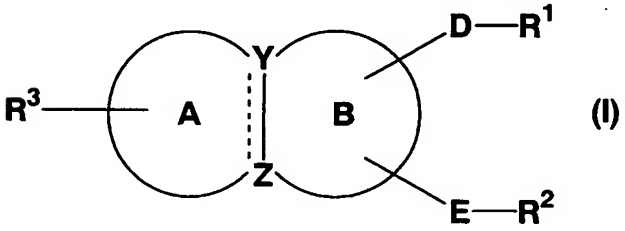


[wherein, all symbols have the same meanings as in the above (1)], a pharmaceutically acceptable salt thereof, a solvate thereof or a prodrug thereof,

(5) the agent described in the above (4), which is an agent for the prevention and/or treatment of a respiratory disease,

(6) the agent described in the above (5), which is an agent for the prevention of asthma,

(7) a pharmaceutical composition comprising the compound of formula (I)



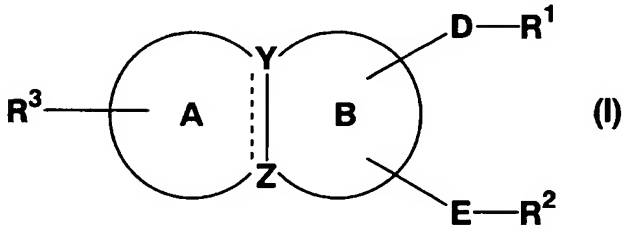
[wherein, all symbols have the same meanings as in the above (1)], a pharmaceutically acceptable salt thereof, a solvate thereof or a prodrug thereof,

(8) the pharmaceutical composition described in the above (7), which is a cysLT$_2$ receptor antagonistic agent,

(9) the pharmaceutical composition described in the above (8), which is combined with one or

more member(s) selected from a $cysLT_1$ receptor antagonist, a steroidal agent and a sympathomimetic agent,

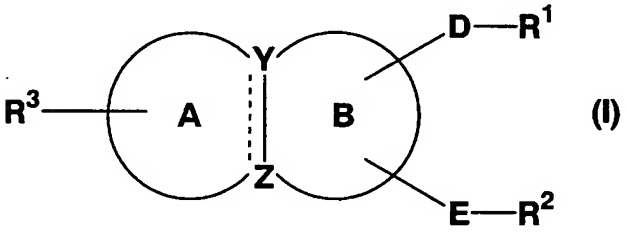
(10) a method for the antagonizing $cycLT_2$ receptor, characterized by administering to a mammal an effective amount of the compound of formula (I)



[wherein, all symbols have the same meanings as in the above (1)], a pharmaceutically acceptable salt thereof, a solvate thereof or a prodrug thereof described in the above (1),

(11) the method described in the above (10), which is the method for the prevention and/or treatment of a respiratory disease,

(12) use of the compound of formula (I)



[wherein, all symbols have the same meanings as in the above (1)], a pharmaceutically acceptable salt thereof, a solvate thereof or a prodrug thereof for the manufacture of an antagonistic agent of $cysLT_2$ receptor,

(13) the use described in the above (12), which is the use for the manufacture of an agent for the prevention and/or treatment of a respiratory disease, and

(14) a pharmaceutical composition comprising the compound having $cysLT_2$ receptor antagonistic activity.

In the present specification, the cyclic group in the cyclic group which may have substituent(s) represented by A is, C3-15 carbocyclic ring, or 3-15 membered mono-, bi- or tri-cyclic partially or completely saturated aromatic heterocyclic ring comprising 1-5 of hetero atom selected from oxygen, nitrogen and/or sulfur.

In the present specification, C3-15 carbocyclic ring includes, C3-15 mono-, bi- or tri-cyclic aromatic carbocyclic ring, partially or completely saturated one thereof, spiro bi-cyclic carbocyclic ring and bridged carbocyclic ring, e.g. cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclooctane, cyclononane, cyclodecane, cycloundecane, cyclododecane, cyclotridecane, cyclotetradecane, cyclopentadecane, cyclopentene, cyclohexene, cycloheptene, cyclooctene, cyclopentadiene, cyclohexadiene, cycloheptadiene, cyclooctadiene,

benzene, pentalene, perhydropentalene, azulene, perhydroazulene, indene, perhydroindene, indan, naphthalene, dihydronaphthalene, tetrahydronaphthalene, perhydronaphthalene, heptalene, perhydroheptalene, biphenylene, as-indacene, s-indacene, acenaphthylene, acenaphthene, fluorene, phenalene, phenanthrene, anthracene, spiro[4.4]nonane, spiro[4.5]decane, spiro[5.5]undecane, bicyclo[2.2.1]heptane, bicyclo[2.2.1]hept-2-ene, bicyclo[3.1.1]heptane, bicyclo[3.1.1]hept-2-ene, bicyclo[2.2.2]octane, bicyclo[2.2.2]oct-2-ene, adamantane or noradamantane ring, etc.

In the present specificatioin, the 3-15 membered mono-, bi- or tri-cyclic optionally partially or completely saturated aromatic heterocyclic ring comprising 1-5 of hetero atom selected from oxygen, nitrogen and/or sulfur includes, e.g. pyrrole, imidazole, triazole, tetrazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, azepine, diazepine, furan, pyran, oxepin, thiophene, thiopyran, thiepin, oxazole, isoxazole, thiazole, isothiazole, furazane, oxadiazole, oxazine, oxadiazine, oxazepine, oxadiazepine, thiadiazole, thiazine, thiadiazine, thiazepine, thiadiazepine, indole, isoindole, indolizine, benzofuran, isobenzofuran, benzothiophene, isobenzothiophene, dithianaphthalene, indazole, quinoline, isoquinoline, quinolizine, purine, phthalazine, pteridine, naphthyridine, quinoxaline, quinazoline, cinnoline, benzoxazole, benzothiazole, benzimidazole, chromene, benzoxepine, benzoxazepine, benzoxadiazepine, benzothiepine, benzothiazepine, benzothiadiazepine, benzazepine, benzodiazepine, benzofurazane, benzothiadiazole, benzotriazole, carbazole, β-carboline, acridine, phenazine, dibenzofuran, xanthene, dibenzothiophene, phenothiazine, phenoxazine, phenoxathiin, thianthrene, phenanthridine, phenanthroline, perimidine, pyrazolopyridine, aziridine, azetidine, pyrroline, pyrrolidine, imidazoline, imidazolidine, triazoline, triazolidine, tetrazoline, tetrazolidine, pyrazoline, pyrazolidine, dihydropyridine, tetrahydropyridine, piperidine, dihydropyrazine, tetrahydropyrazine, piperazine, dihydropyrimidine, tetrahydropyrimidine, perhydropyrimidine, dihydropyridazine, tetrahydropyridazine, perhydropyridazine, dihydroazepine, tetrahydroazepine, perhydroazepine, dihydrodiazepine, tetrahydrodiazepine, perhydrodiazepine, oxirane, oxetane, dihydrofuran, tetrahydrofuran, dihydropyran, tetrahydropyran, dihydrooxepin, tetrahydrooxepin, perhydrooxepin, thiirane, thietane dihydrothiophene, tetrahydrothiophene, dihydrothiopyran, tetrahydrothiopyran, dihydrothiepin, tetrahydrothiepin, perhydrothiepin, dihydrooxazole, tetrahydrooxazole (oxazolidine), dihydroisoxazole, tetrahydroisoxazole (isoxazolidine), dihydrothiazole, tetrahydrothiazole (thiazolidine), dihydroisothiazole, tetrahydroisothiazole (isothiazolidine), dihydrofurazane, tetrahydrofurazane, dihydrooxadiazole, tetrahydrooxadiazole (oxadiazolidine), dihydrooxazine, tetrahydrooxazine, dihydrooxadiazine, tetrahydrooxadiazine, dihydrooxazepine, tetrahydrooxazepine, perhydrooxazepine, dihydrooxadiazepine, tetrahydrooxadiazepine, perhydrooxadiazepine, dihydrothiadiazole, tetrahydrothiadiazole (thiadiazolidine), dihydrothiazine, tetrahydrothiazine, dihydrothiadiazine,

tetrahydrothiadiazine, dihydrothiazepine, tetrahydrothiazepine, perhydrothiazepine, dihydrothiadiazepine, tetrahydrothiadiazepine, perhydrothiadiazepine, morpholine, thiomorpholine, oxathiane, indoline, isoindoline, dihydrobenzofuran, perhydrobenzofuran, dihydroisobenzofuran, perhydroisobenzofuran, dihydrobenzothiophene, perhydrobenzothiophene, dihydroisobenzothiophene, perhydroisobenzothiophene, dihydroindazole, perhydroindazole, dihydroquinoline, tetrahydroquinoline, perhydroquinoline, dihydroisoquinoline, tetrahydroisoquinoline, perhydroisoquinoline, dihydrophthalazine, tetrahydrophthalazine, perhydrophthalazine, dihydronaphthyridine, tetrahydronaphthyridine, perhydronaphthyridine, dihydroquinoxaline, tetrahydroquinoxaline, perhydroquinoxaline, dihydroquinazoline, tetrahydroquinazoline, perhydroquinazoline, dihydrocinnoline, tetrahydrocinnoline, perhydrocinnoline, benzoxathiane, dihydrobenzoxazine, dihydrobenzothiazine, pyrazinomorpholine, dihydrobenzoxazole, perhydrobenzoxazole, dihydrobenzothiazole, perhydrobenzothiazole, dihydrobenzimidazole, perhydrobenzimidazole, dihydrobenzazepine, tetrahydrobenzazepine, dihydrobenzodiazepine, tetrahydrobenzodiazepine, benzodioxepane, dihydrobenzoxazepine, tetrahydrobenzoxazepine, dihydrocarbazole, tetrahydrocarbazole, perhydrocarbazole, dihydroacridine, tetrahydroacridine, perhydroacridine, dihydrodibenzofuran, dihydrodibenzothiophene, tetrahydrodibenzofuran, tetrahydrodibenzothiophene, perhydrodibenzofuran, perhydrodibenzothiophene, dioxolane, dioxane, dithiolane, dithiane, dioxaindan, benzodioxane, chroman, benzodithiolane, benzodithiane, azaspiro[4.4]nonane, oxazaspiro[4.4]nonane, dioxaspiro[4.4]nonane, azaspiro[4.5]decane, thiaspiro[4.5]decane, dithiaspiro[4.5]decane, dioxaspiro[4.5]decane, oxazaspiro[4.5]decane, azaspiro[5.5]undecane, oxaspiro[5.5]undecane, dioxaspiro[5.5]undecane, azabicyclo[2.2.1]heptane, oxabicyclo[2.2.1]heptane, azabicyclo[3.1.1]heptane, azabicyclo[3.2.1]octane, oxabicyclo[3.2.1]octane, azabicyclo[2.2.2]octane, diazabicyclo[2.2.2]octane, tetrahydro-β-carboline, hexahydroazepinoindole, oxazaspiro[2.5]octane, hexahydroazepinoindazole, hexahydropyrazolopyridoazepine, tetrahydropyrazoloisoquinoline or tetrahydropyrazolonaphthyridine ring, etc.

In the present specification, the "substituent" in the cyclic group which may have substituent(s) represented by A includes, for example, (1) alkyl which may have substituent(s), (2) alkenyl which may have substituent(s), (3) alkynyl which may have substituent(s), (4) carbocyclic ring which may have substituent(s), (5) heterocyclic ring which may have substituent(s), (6) hydroxy which may be protected, (7) thiol which may be protected, (8) amino which may be protected, (9) carbamoyl which may have substituent(s), (10) sulfamoyl which may have substituent(s), (11) carboxy, (12) alkoxycarbonyl (e.g. C1-6 alkoxycarbonyl such as methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl, etc.), (13) sulfo (-SO_3H), (14) sulfino, (15) phosphono, (16) nitro, (17) cyano, (18) amidino, (19)imino, (20) -$B(OH)_2$, (21) halogen (e.g. fluorine,

chlorine, bromine, iodine, etc.), (22) alkylsulfinyl (e.g. C1-4 alkylsulfinyl such as methylsulfinyl, ethylsulfinyl, etc.), (23) aromatic ring-sulfinyl (e.g. C6-10 aromatic ring-sulfinyl such as phenylsulfinyl etc.), (24) alkylsulfonyl (e.g. C1-4 alkylsulfonyl such as methylsulfonyl, ethylsulfonyl, etc.), (25) aromatic ring-sulfonyl (e.g. C6-10 aromatic ring-sulfonyl such as phenylsulfonyl etc.), (26) acyl (e.g. C1-6 alkanoyl such as formyl, acetyl, propanoyl, pivaloyl etc.), (27) oxo, (28) thioxo, (29) (C1-6 alkoxyimino)methyl (e.g. (methoxyimino)methyl, etc.), etc., and 1-5 of these substituents may be positioned where acceptable.

The alkyl in the "alkyl which may have substituent(s)" as a substituent includes straight or branched C1-20 alkyl such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, octadecyl, nonadecyl, icosyl, etc. Hereby the substituent of the alkyl includes, for example, hydroxy, amino, carboxy, nitro, azido, mono- or di-C1-6 alkylamino (e.g. methylamino, ethylamino, propylamino, dimethylamino, diethylamino, etc.), N-aromatic ring-amino (e.g. N-phenylamino etc.), N-aromatic ring-N-alkylamino (e.g. N-phenyl-N-methylamino, N-phenyl-N-ethylamino, N-phenyl-N-propylamino, N-phenyl-N-butylamino, N-phenyl-N-pentylamino, N-phenyl-N-hexylamino, etc.), acylamino, N-acyl-N-alkylamino, C1-6 alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, hexyloxy, etc.), C3-7 cycloalkyl-C1-6 alkoxy (e.g. cyclohexylmethyloxy, cyclopentylethyloxy, etc.), C3-7 cycloalkyloxy (e.g. cyclohexyloxy etc.), C7-15 aralkyloxy (e.g. benzyloxy, phenethyloxy, phenylpropyloxy, naphthylmethyloxy, naphthylethyloxy, etc.), phenoxy, C1-6 alkoxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl, etc.), C1-6 alkylcarbonyloxy (e.g. acetoxy, ethylcarbonyloxy, etc.), C1-4 alkylthio (e.g. methylthio, ethylthio, propylthio, butylthio, etc.), halogen (fluorine, chlorine, bromine, iodine), alkylsulfonyl (e.g. C1-4 alkylsulfonyl such as methylsulfonyl, ethylsulfonyl, etc.), aromatic ring-sulfonyl (e.g. C6-10 aromatic ring-sulfonyl such as phenylsulfonyl etc.), acyl, (e.g. C1-6 alkanoyl such as formyl, acetyl, propanoyl, pivaloyl etc., C6-10 aromatic ring carbonyl such as benzoyl etc.), carbocyclic ring which may have substituent(s), heterocyclic ring which may have substituent(s), etc. and 1-4 of these substituents may be positioned where acceptable.

Hereby, the acyl in the acyl, acylamino and N-acyl-N-alkylamino as a substituent of alkyl has the same meaning as the acyl as a protective group in “hydroxyl which may be protected”, “thiol which may be protected” and “amino which may be protected” as a substituent hereafter described. And the "alkyl" in the N-acyl-N-alkylamino includes, for example, straight or branched C1-20 alkyl such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, octadecyl, nonadecyl, icosyl, etc.

The carbocyclic ring as the substituent of alkyl includes, for example, C3-15 mono-, bi- or

tri-cyclic optionally partially or completely saturated aromatic carbocyclic ring etc. C3-15 mono-, bi- or tri-cyclic optionally partially or completely saturated aromatic carbocyclic ring includes, for example, cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclooctane, cyclononane, cyclodecane, cycloundecane, cyclododecane, cyclotridecane, cyclotetradecane, cyclopentadecane, cyclopentene, cyclohexene, cycloheptene, cyclooctene, cyclopentadiene, cyclohexadiene, cycloheptadiene, cyclooctadiene, benzene, pentalene, perhydropentalene, azulene, perhydroazulene, indene, perhydroindene, indan, naphthalene, dihydronaphthalene, tetrahydronaphthalene, perhydronaphthalene, heptalene, perhydroheptalene, biphenylene, as-indacene, s-indacene, acenaphthylene, acenaphthene, fluorene, phenalene, phenanthrene, anthracene etc. In addition, C3-15 mono-, bi- or tri-cyclic optionally partially or completely saturated aromatic carbocyclic ring includes spiro bi-cyclic carbocyclic ring and bridged bi-cyclic carbocyclic ring. They includes, for example, spiro[4.4]nonane, spiro[4.5]decane, spiro[5.5]undecane, bicyclo[2.2.1]heptane, bicyclo[2.2.1]hept-2-ene, bicyclo[3.1.1]heptane, bicyclo[3.1.1]hept-2-ene, bicyclo[2.2.2]octane, bicyclo[2.2.2]oct-2-ene, adamantane or noradamantane ring, etc.

Hereby the substituent in the carbocyclic ring as the substituent of alkyl includes C1-8 alkyl (e.g., methyl ethyl, propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, heptyl, octyl etc.), hydroxyl, amino, carboxyl, nitro, mono-, or di-C1-6 alkylamino (e.g., methylamino, ethylamino, propylamino, dimethylamino, diethylamino etc.), C1-6 alkoxy (e.g., methoxy, ethoxy, propoxy, hexyloxy etc.), C1-6 alkoxycarbonyl (e.g, methoxycarbonyl, ethoxycarbonyl, tert-butoxycarobonyl etc.), C1-6 alkylcarbnyloxy (e.g., acetoxy, ethylcarbonyloxy etc.), C1-4 alkylthio (e.g., methylthio, ethylthio, propylthio, butylthio etc.), halogen atom (fluorine, chlorine, bromine, iodine), trihalomethyl (e.g.,trifluoromethyl etc.), etc., and 1-4 of these substituents may be positioned where acceptable.

The heterocyclic ring as the substituent of alkyl includes, for example, 3-15 membered mono-, bi- or tri-cyclic optionally partially or completely saturated aromatic heterocyclic ring comprising 1-5 of hetero atom selected from oxygen, nitrogen and/or sulfur etc. Among 3-15 membered mono-, bi- or tri-cyclic partially or completely saturated aromatic heterocyclic ring comprising 1-5 of hetero atom selected from oxygen, nitrogen and/or sulfur, 3-15 membered mono-, bi- or tri-cyclic aromatic heterocyclic ring comprising 1-5 of hetero atom selected from oxygen, nitrogen and/or sulfur includes, for example, pyrrole, imidazole, triazole, tetrazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, azepine, diazepine, furan, pyran, oxepin, thiophene, thiopyran, thiepin, oxazole, isoxazole, thiazole, isothiazole, furazane, oxadiazole, oxazine, oxadiazine, oxazepine, oxadiazepine, thiadiazole, thiazine, thiadiazine, thiazepine, thiadiazepine, indole, isoindole, indolizine, benzofuran, isobenzofuran, benzothiophene, isobenzothiophene, dithianaphthalene, indazole, quinoline, isoquinoline, quinolizine, purine,

phthalazine, pteridine, naphthyridine, quinoxaline, quinazoline, cinnoline, benzoxazole, benzothiazole, benzimidazole, chromene, benzoxepine, benzoxazepine, benzoxadiazepine, benzothiepine, benzothiazepine, benzothiadiazepine, benzazepine, benzodiazepine, benzofurazane, benzothiadiazole, benzotriazole, carbazole, β-carboline, acridine, phenazine, dibenzofuran, xanthene, dibenzothiophene, phenothiazine, phenoxazine, phenoxathiin, thianthrene, phenanthridine, phenanthroline, perimidine etc. Among 3-15 membered mono-, bi- or tri-cyclic optionally partially or completely saturated aromatic heterocyclic ring comprising 1-5 of hetero atom selected from oxygen, nitrogen and/or sulfur, 3-15 membered mono-, bi- or tri-cyclic partially or completely saturated aromatic heterocyclic ring comprising 1-5 of hetero atom selected from oxygen, nitrogen and/or sulfur includes, for example, aziridine, azetidine, pyrroline, pyrrolidine, imidazoline, imidazolidine, triazoline, triazolidine, tetrazoline, tetrazolidine, pyrazoline, pyrazolidine, dihydropyridine, tetrahydropyridine, piperidine, dihydropyrazine, tetrahydropyrazine, piperazine, dihydropyrimidine, tetrahydropyrimidine, perhydropyrimidine, dihydropyridazine, tetrahydropyridazine, perhydropyridazine, dihydroazepine, tetrahydroazepine, perhydroazepine, dihydrodiazepine, tetrahydrodiazepine, perhydrodiazepine, oxirane, oxetane, dihydrofuran, tetrahydrofuran, dihydropyran, tetrahydropyran, dihydrooxepin, tetrahydrooxepin, perhydrooxepin, thiirane, thietane dihydrothiophene, tetrahydrothiophene, dihydrothiopyran, tetrahydrothiopyran, dihydrothiepin, tetrahydrothiepin, perhydrothiepin, dihydrooxazole, tetrahydrooxazole (oxazolidine), dihydroisoxazole, tetrahydroisoxazole (isoxazolidine), dihydrothiazole, tetrahydrothiazole (thiazolidine), dihydroisothiazole, tetrahydroisothiazole (isothiazolidine), dihydrofurazane, tetrahydrofurazane, dihydrooxadiazole, tetrahydrooxadiazole (oxadiazolidine), dihydrooxazine, tetrahydrooxazine, dihydrooxadiazine, tetrahydrooxadiazine, dihydrooxazepine, tetrahydrooxazepine, perhydrooxazepine, dihydrooxadiazepine, tetrahydrooxadiazepine, perhydrooxadiazepine, dihydrothiadiazole, tetrahydrothiadiazole (thiadiazolidine), dihydrothiazine, tetrahydrothiazine, dihydrothiadiazine, tetrahydrothiadiazine, dihydrothiazepine, tetrahydrothiazepine, perhydrothiazepine, dihydrothiadiazepine, tetrahydrothiadiazepine, perhydrothiadiazepine, morpholine, thiomorpholine, oxathiane, indoline, isoindoline, dihydrobenzofuran, perhydrobenzofuran, dihydroisobenzofuran, perhydroisobenzofuran, dihydrobenzothiophene, perhydrobenzothiophene, dihydroisobenzothiophene, perhydroisobenzothiophene, dihydroindazole, perhydroindazole, dihydroquinoline, tetrahydroquinoline, perhydroquinoline, dihydroisoquinoline, tetrahydroisoquinoline, perhydroisoquinoline, dihydrophthalazine, tetrahydrophthalazine, perhydrophthalazine, dihydronaphthyridine, tetrahydronaphthyridine, perhydronaphthyridine, dihydroquinoxaline, tetrahydroquinoxaline, perhydroquinoxaline, dihydroquinazoline, tetrahydroquinazoline, perhydroquinazoline, dihydrocinnoline, tetrahydrocinnoline,

perhydrocinnoline, benzoxathiane, dihydrobenzoxazine, dihydrobenzothiazine, pyrazinomorpholine, dihydrobenzoxazole, perhydrobenzoxazole, dihydrobenzothiazole, perhydrobenzothiazole, dihydrobenzimidazole, perhydrobenzimidazole, dihydrobenzazepine, tetrahydrobenzazepine, dihydrobenzodiazepine, tetrahydrobenzodiazepine, benzodioxepane, dihydrobenzoxazepine, tetrahydrobenzoxazepine, dihydrocarbazole, tetrahydrocarbazole, perhydrocarbazole, dihydroacridine, tetrahydroacridine, perhydroacridine, dihydrodibenzofuran, dihydrodibenzothiophene, tetrahydrodibenzofuran, tetrahydrodibenzothiophene, perhydrodibenzofuran, perhydrodibenzothiophene, dioxolane, dioxane, dithiolane, dithiane, dioxaindan, benzodioxane, chroman, benzodithiolane, benzodithiane etc. Hereby, the substituent in the heterocyclic ring as the substituent of alkyl includes C1-8 alkyl (e.g., methyl ethyl, propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, heptyl, octyl etc.), hydroxyl, amino, carboxyl, nitro, mono-, or di-C1-6 alkylamino (e.g., methylamino, ethylamino, propylamino, dimethylamino, diethylamino etc.), C1-6 alkoxy (e.g., methoxy, ethoxy, propoxy, hexyloxy etc.), C1-6 alkoxycarbonyl (e.g, methoxycarbonyl, ethoxycarbonyl, tert-butoxycarobonyl etc.), C1-6 alkylcarbnyloxy (e.g., acetoxy, ethylcarbonyloxy etc.), C1-4 alkylthio (e.g., methylthio, ethylthio, propylthio, butylthio etc.), halogen atom (fluorine, chlorine, bromine, iodine), etc., and 1-4 of these substituents may be positioned where acceptable.

The alkenyl in "the alkenyl which may have substituent(s)" as substituent includes, for example, straight or branched C2-20 alkenyl such as ethenyl, propenyl, butenyl, pentenyl, hexenyl etc. Hereby, the substituent(s) of alkenyl has the same meanings as the substituent in the above described "alkyl which may have substituent(s)".

The alkynyl in "the alkynyl which may have substituent(s)" as substituent includes, for example, straight or branched C2-20 alkynyl such as ethynyl, propynyl, butynyl, pentynyl, hexynyl etc. Hereby, the substituent(s) of alkynyl has the same meanings as the substituent in the above described "alkyl which may have substituent(s)".

The carbocyclic ring as "the carbocyclic ring which may have substituent(s)" includes, for example, C3-15 mono-, bi- or tri-cyclic optionally partially or completely saturated aromatic carbocyclic ring etc. C3-15 mono-, bi- or tri-cyclic optionally partially or completely saturated aromatic carbocyclic ring includes, for example, cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclooctane, cyclononane, cyclodecane, cycloundecane, cyclododecane, cyclotridecane, cyclotetradecane, cyclopentadecane, cyclopentene, cyclohexene, cycloheptene, cyclooctene, cyclopentadiene, cyclohexadiene, cycloheptadiene, cyclooctadiene, benzene, pentalene, perhydropentalene, azulene, perhydroazulene, indene, perhydroindene, indan, naphthalene, dihydronaphthalene, tetrahydronaphthalene, perhydronaphthalene, heptalene, perhydroheptalene, biphenylene, as-indacene, s-indacene, acenaphthylene,

acenaphthene, fluorene, phenalene, phenanthrene, anthracene etc. In addition, C3-15 mono-, bi- or tri-cyclic partially or completely saturated aromatic carbocyclic ring includes spiro bi-cyclic carbocyclic ring and bridged bi-cyclic carbocyclic ring. It includes, for example, spiro[4.4]nonane, spiro[4.5]decane, spiro[5.5]undecane, bicyclo[2.2.1]heptane, bicyclo[2.2.1]hept-2-ene, bicyclo[3.1.1]heptane, bicyclo[3.1.1]hept-2-ene, bicyclo[2.2.2]octane, bicyclo[2.2.2]oct-2-ene, adamantane or noradamantane ring, etc.

Hereby the substituent in the carbocyclic ring as the substituent of alkyl includes C1-4 alkyl (e.g., methyl ethyl, propyl, isopropyl, butyl etc.), C2-4 alkenyl (e.g. ethenyl, propenyl, butenyl etc.), C2-4 alkynyl (e.g. ethynyl, propynyl, butynyl etc.), hydroxyl, C1-4 alkoxy (e.g., methoxy, ethoxy, propoxy, butoxy etc.), C1-6 alkoxycarbonyl (e.g, methoxycarbonyl, ethoxycarbonyl, tert-butoxycarobonyl etc.), thiol, C1-4 alkylthio (e.g., methylthio, ethylthio, propylthio, butylthio etc.), amino, mono-, or di-C1-6 alkylamino (e.g., methylamino, ethylamino, propylamino, dimethylamino, diethylamino etc.), halogen atom (fluorine, chlorine, bromine, iodine), trihalomethyl (e.g.,trifluoromethyl etc.), trihalomethoxy (e.g., trifluoromethoxy etc.), trihalomethylthio (e.g., trifluoromethylthio etc.), dihalomethylthio (e.g., difluoromethylthio etc.), cyclic ring which may have a substituent(s), cyano, nitro etc., and 1-4 of these substituents may be positioned where acceptable.

Hereby, the cyclic group which may have substituent(s) as the substituent of carbocyclic ring in the "carbocyclic ring which may have substituent(s)" as the substituent has the same meanings as "cyclic group" in the cyclic group which may have substituent(s) represented by the above described A. The substituent of the cyclic group which may have a subsituent(s) as the substituent of carbocyclic group in "the carbocyclic ring which may have a substituent(s)" as the substituent has the same meanings as the substituent of carbocyclic ring as the substituent of "the alkyl which may have a substituent(s)" as the above described substituent and 1-4 of these arbitrary substituents may be positioned where acceptable. The heterocyclic ring in "the heterocyclic ring which may have a substituent(s)" as the substituent includes, for example, the 3-15 membered mono-, bi- or tri-cyclic optionally partially or completely saturated aromatic heterocyclic ring comprising 1-5 of hetero atom selected from oxygen, nitrogen and/or sulfur etc. Among 3-15 membered mono-, bi- or tri-cyclic optionally partially or completely saturated aromatic heterocyclic ring comprising 1-5 of hetero atom selected from oxygen, nitrogen and/or sulfur, 3-15 membered mono-, bi- or tri-cyclic aromatic heterocyclic ring comprising 1-5 of hetero atom selected from oxygen, nitrogen and/or sulfur includes, for example, pyrrole, imidazole, triazole, tetrazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, azepine, diazepine, furan, pyran, oxepin, thiophene, thiopyran, thiepin, oxazole, isoxazole, thiazole, isothiazole, furazane, oxadiazole, oxazine, oxadiazine, oxazepine, oxadiazepine, thiadiazole, thiazine, thiadiazine, thiazepine, thiadiazepine, indole, isoindole, indolizine, benzofuran,

isobenzofuran, benzothiophene, isobenzothiophene, dithianaphthalene, indazole, quinoline, isoquinoline, quinolizine, purine, phthalazine, pteridine, naphthyridine, quinoxaline, quinazoline, cinnoline, benzoxazole, benzothiazole, benzimidazole, chromene, benzoxepine, benzoxazepine, benzoxadiazepine, benzothiepine, benzothiazepine, benzothiadiazepine, benzazepine, benzodiazepine, benzofurazane, benzothiadiazole, benzotriazole, carbazole, β-carboline, acridine, phenazine, dibenzofuran, xanthene, dibenzothiophene, phenothiazine, phenoxazine, phenoxathiin, thianthrene, phenanthridine, phenanthroline, perimidine etc. Among 3-15 membered mono-, bi- or tri-cyclic optionally partially or completely saturated aromatic heterocyclic ring comprising 1-5 of hetero atom selected from oxygen, nitrogen and/or sulfur, 3-15 membered mono-, bi- or tri-cyclic heterocyclic ring partially or fully saturated comprising 1-5 of hetero atom selected from oxygen, nitrogen and/or sulfur includes, for example, aziridine, azetidine, pyrroline, pyrrolidine, imidazoline, imidazolidine, triazoline, triazolidine, tetrazoline, tetrazolidine, pyrazoline, pyrazolidine, dihydropyridine, tetrahydropyridine, piperidine, dihydropyrazine, tetrahydropyrazine, piperazine, dihydropyrimidine, tetrahydropyrimidine, perhydropyrimidine, dihydropyridazine, tetrahydropyridazine, perhydropyridazine, dihydroazepine, tetrahydroazepine, perhydroazepine, dihydrodiazepine, tetrahydrodiazepine, perhydrodiazepine, oxirane, oxetane, dihydrofuran, tetrahydrofuran, dihydropyran, tetrahydropyran, dihydrooxepin, tetrahydrooxepin, perhydrooxepin, thiirane, thietane dihydrothiophene, tetrahydrothiophene, dihydrothiopyran, tetrahydrothiopyran, dihydrothiepin, tetrahydrothiepin, perhydrothiepin, dihydrooxazole, tetrahydrooxazole (oxazolidine), dihydroisoxazole, tetrahydroisoxazole (isoxazolidine), dihydrothiazole, tetrahydrothiazole (thiazolidine), dihydroisothiazole, tetrahydroisothiazole (isothiazolidine), dihydrofurazane, tetrahydrofurazane, dihydrooxadiazole, tetrahydrooxadiazole (oxadiazolidine), dihydrooxazine, tetrahydrooxazine, dihydrooxadiazine, tetrahydrooxadiazine, dihydrooxazepine, tetrahydrooxazepine, perhydrooxazepine, dihydrooxadiazepine, tetrahydrooxadiazepine, perhydrooxadiazepine, dihydrothiadiazole, tetrahydrothiadiazole (thiadiazolidine), dihydrothiazine, tetrahydrothiazine, dihydrothiadiazine, tetrahydrothiadiazine, dihydrothiazepine, tetrahydrothiazepine, perhydrothiazepine, dihydrothiadiazepine, tetrahydrothiadiazepine, perhydrothiadiazepine, morpholine, thiomorpholine, oxathiane, indoline, isoindoline, dihydrobenzofuran, perhydrobenzofuran, dihydroisobenzofuran, perhydroisobenzofuran, dihydrobenzothiophene, perhydrobenzothiophene, dihydroisobenzothiophene, perhydroisobenzothiophene, dihydroindazole, perhydroindazole, dihydroquinoline, tetrahydroquinoline, perhydroquinoline, dihydroisoquinoline, tetrahydroisoquinoline, perhydroisoquinoline, dihydrophthalazine, tetrahydrophthalazine, perhydrophthalazine, dihydronaphthyridine, tetrahydronaphthyridine, perhydronaphthyridine, dihydroquinoxaline, tetrahydroquinoxaline, perhydroquinoxaline, dihydroquinazoline,

tetrahydroquinazoline, perhydroquinazoline, dihydrocinnoline, tetrahydrocinnoline, perhydrocinnoline, benzoxathiane, dihydrobenzoxazine, dihydrobenzothiazine, pyrazinomorpholine, dihydrobenzoxazole, perhydrobenzoxazole, dihydrobenzothiazole, perhydrobenzothiazole, dihydrobenzimidazole, perhydrobenzimidazole, dihydrobenzazepine, tetrahydrobenzazepine, dihydrobenzodiazepine, tetrahydrobenzodiazepine, benzodioxepane, dihydrobenzoxazepine, tetrahydrobenzoxazepine, dihydrocarbazole, tetrahydrocarbazole, perhydrocarbazole, dihydroacridine, tetrahydroacridine, perhydroacridine, dihydrodibenzofuran, dihydrodibenzothiophene, tetrahydrodibenzofuran, tetrahydrodibenzothiophene, perhydrodibenzofuran, perhydrodibenzothiophene, dioxolane, dioxane, dithiolane, dithiane, dioxaindan, benzodioxane, chroman, benzodithiolane, benzodithiane etc.

Hereby, the substituent of heterocyclic ring has the same meanings as the substituent in the above described "the carbocyclic ring which may have a substituent(s)" and 1-4 of these arbitrary substituents may be positioned where acceptable.

The protective group in "the hydroxyl group which may be protected", "the thiol group which may be protected" and "the amino group which may be protected" as the substituent includes, for example, alkyl which may have substituent(s) (it has the same meaning as the above "alkyl which may have substituent(s)"), carbocyclic ring which may have substituent(s) (it has the same meaning as the above "carbocyclic ring which may have substituent(s)"), heterocyclic ring which may have substituent(s) (it has the same meaning as the above "a heterocyclic ring which may have substituent(s)"), alkylsulfonyl (e.g. C1-4 alkylsulfonyl such as methylsulfonyl, ethylsulfonyl, etc.), aromatic ring-sulfonyl (e.g. C6-10 aromatic ring-sulfonyl such as phenylsulfonyl, etc.), acyl, etc.

Hereby, the acyl includes, for example, (1) alkylcarbonyl which may have substituent(s) (2) alkenylcarbonyl which may have substituent(s) (3) alkynylcarbonyl which may have substituent(s), (4) carbocylic ring-carbonyl which may have substituent(s) (5) heterocylic ring-carbonyl which may have substituent(s)etc, and 1-4 of these arbitrary substituents may be positioned where acceptable.

The alkyl which may have substituent(s) in "the alkylcarbonyl which may have substituent(s)" has the same meaning as the above "alkyl which may have substituent(s)". The alkenyl which may have substituent(s) in "alkenylcarbonyl which may have substituent(s)" has the same meaning as the above "alkenyl which may have substituent(s)". The alkynyl which may have substituent(s) in "the alkynylcarbonyl which may have substituent(s)" has the same meaning as the above "alkynyl which may have substituent(s)". The carbocylic ring-which may have substituent(s) in "carbocylic ring-carbonyl" has the same meaning as the above "carbocylic ring which may have substituent(s)".The heterocylic ring which may have substituent(s) in "heterocylic ring-carbonyl" has the same meaning as the above "heterocylic ring which may

have substituent(s)").

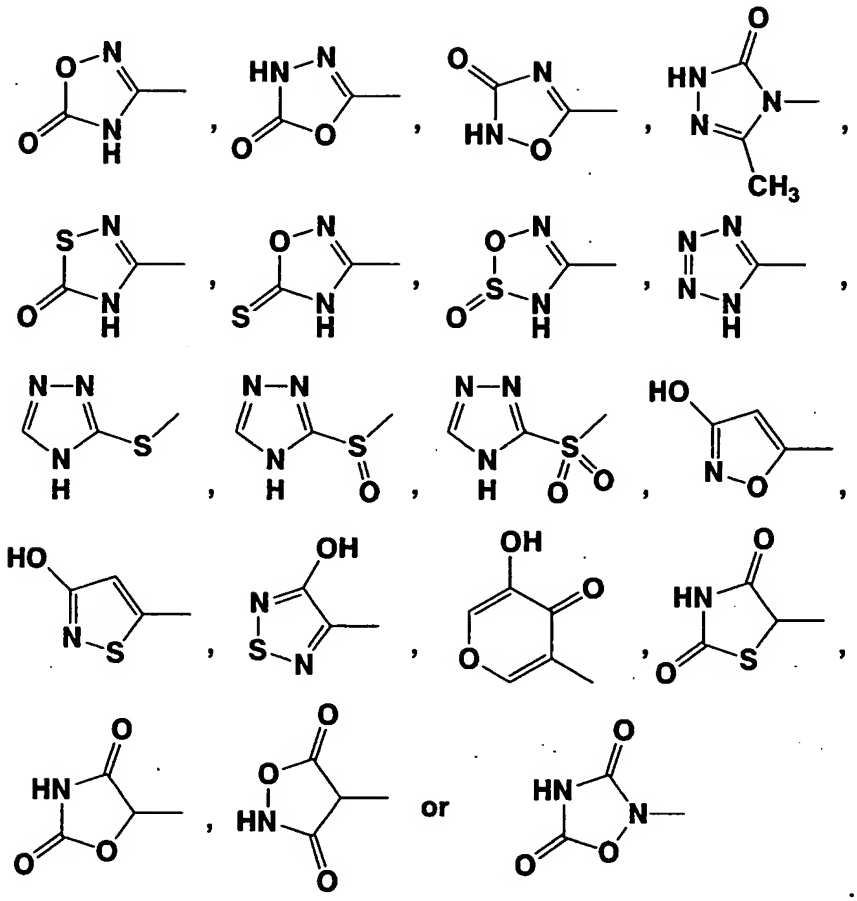
The "carbamoyl which may have substituent(s)" as a substituent includes, for example, unsubstituted carbamoyl, N-mono-C1-4 alkylcarbamoyl (e.g. N-methylcarbamoyl, N-ethylcarbamoyl, N-propylcarbamoyl, N-isopropylcarbamoyl, N-butylcarbamoyl, etc.), N,N-di-C1-4 alkylcarbamoyl (e.g. N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N,N-dipropylcarbamoyl, N,N-dibutylcarbamoyl, etc.), 1-piperidylcarbonyl, etc.

The "sulfamoyl which may have substituent(s)" as a substituent includes, for example, unsubstituted sulfamoyl, N-mono-C1-4 alkylsulfamoyl (e.g. N-methylsulfamoyl, N-ethylsulfamoyl, N-propylsulfamoyl, N-isopropylsulfamoyl, N-butylsulfamoyl, etc.), N,N-di-C1-4 alkylsulfamoyl (e.g. N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N,N-dipropylsulfamoyl, N,N-dibutylsulfamoyl, etc.), etc.

In the present specification, the "cyclic group" in the cyclic group which may have a substituent(s) represented by B has the same meanings as the cyclic group in the above "cyclic group which may have a substituent(s) represented by A".

In the present specification, the "substituent" in the cyclic group which may have a substituent(s) represented by B has the same meanings as the substituent in the above "cyclic group which may have a substituent(s) represented by A".

In the present specification, the "acidic group" represented by R^1 and R^2 means an acidic group which may be protected by protective group(s). The "acidic group" in the acidic group which may be protected by protective group(s) includes various kinds of Brönsted acid, e.g. carboxy (-COOH), hydroxamic acid (-CONHOH), acylcyanamide (-CONHCN), sulfo ($-SO_3H$), sulfonamide ($-SO_2NH_2$ or $NR^{100}SO_3H$, wherein R^{100} is hydrogen or hydrocarbon which may have substituent(s) (it has the same meaning as the "hydrocarbon group which may have substituent(s)" in the protective group in the acidic group which may be protected by protective group(s) described hereafter)), acylsulfonamide ($-CONHSO_2R^{100}$ or SO_2NHCOR^{100}, wherein R^{100} has the same meaning as hereinbefore), phosphono ($-P(=O)(OH)_2$), phosphinico ($=P(=O)OH$), amino(hydroxy)phosphoryl ($-P(=O)(OH)(NH_2)$), phenol ($-C_6H_4OH$) or heterocyclic ring residue which comprises a deprotonable hydrogen atom. The "Brönsted acid" represents a substance which gives a hydrogen ion to another substance. The "Heterocyclic ring residue which comprises a deprotonable hydrogen atom" includes, for example,



The "protective group" in the acidic group which may be protected by protective group(s) includes, for example, a hydrocarbon which may have substituent(s), C1-6 alkoxy, optionally protected amino, 1-piperidinyl or 4-morpholinyl, etc.

The "hydrocarbon" group in the "hydrocarbon which may have substituent(s)" includes, for example, C1-15 alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, s-butyl, t-butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, etc.; C3-8 cycloalkyl such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.; C2-10 alkenyl such as vinyl, allyl, 2-methylallyl, 2-butenyl, 3-butenyl, 3-octenyl, etc.; C2-10 alkynyl such as ethynyl, 2-propynyl, 3-hexynyl, etc.; C3-10 cycloalkenyl such as cyclopropenyl, cyclopentenyl, cyclohexenyl, etc.; C6-14 aryl such as phenyl, naphthyl, etc.; C7-16 aralkyl such as benzyl, phenylethyl, etc.; (C3-8 cycloalkyl)-(C1-4 alkyl) such as cyclohexylmethyl, cyclohexylethyl, cyclohexylpropyl, 1-methyl-1-cyclohexylmethyl, etc.

In addition, as the substituent in the "hydrocarbon group which may have substituent(s)" includes, for example, (1) nitro, (2) hydroxy, (3) oxo, (4) thioxo, (5) cyano, (6) carbamoyl, (7) aminocarbonyl substituted by C1-8 hydrocarbon etc. such as N-butylaminocarbonyl, N-cyclohexylmethylaminocarbonyl, N-butyl-N-cyclohexylmethylaminocarbonyl, N-cyclohexylaminocarbonyl, phenylaminocarbonyl, (8) carboxy, (9) C1-4 alkoxycarbonyl such

as methoxycarbonyl, ethoxycarbonyl, etc., (10) sulfo, (11) halogen such as fluorine, chlorine, bromine, iodine, (12) C1-4 lower alkoxy such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, s-butoxy, t-butoxy, etc., (13) phenoxy, (14) halogenophenoxy such as o-, m- or p-chlorophenoxy, o-, m- or p-bromophenoxy, (15) C1-4 lower alkylthio such as methylthio, ethylthio, n-propylthio, isopropylthio, n-butylthio, t-butylthio, etc., (16) phenylthio, (17) C1-4 lower alkylsulfinyl such as methylsulfinyl, ethylsulfinyl, etc., (18) C1-4 lower alkylsulfonyl such as methylsulfonyl, ethylsulfonyl, etc., (19) amino, (20) C1-6 lower acylamino such as acetylamino, propionylamino, etc., (21) primary or secondary amino substituted with hydrocarbon group such as methylamino, ethylamino, n-propylamino, isopropylamino, n-butylamino, dimethylamino, diethylamino, cyclohexylamino, 1-carbamoyl-2-cyclohexylethylamino, N-butyl-N-cyclohexylmethylamino, phenylamino (wherein this "hydrocarbon group" has the same meaning as the above "hydrocarbon group" and it may be substituted with oxo, amino, carbamoyl, etc.), (22) C1-4 lower acyl such as formyl, acetyl, etc., (23) benzoyl, (24) a 5-6 membered heterocyclic ring comprising 1-4 hetero atom selected from oxygen, sulfur, nitrogen, etc. besides carbon atom which may have 1-4 of substituent selected from 1-4 of substituent(s) selected from (a) halogen such as bromine, chlorine, fluorine, etc., (b) hydrocarbon group such as methyl, ethyl, propyl, isopropyl, benzyl, cyclohexyl, cyclohexylmethyl, cyclohexylethyl which may be substituted with oxo, hydroxy, etc., wherein the “hydrocarbon group” as the same meaning as the above “hydrocarbon group”, (c) halogenophenoxy such as o-, m- or p-chlorophenoxy, o-, m- or p-bromophenoxy, etc., and (d) oxo, etc., for example, 2- or 3-thienyl, 2- or 3-furyl, 3-, 4- or 5-pyrazolyl, 4-tetrahydropyranyl, 2-, 4- or 5-thiazolyl, 3-, 4- or 5-isothiazolyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isoxazolyl, 2-, 4- or 5-imidazolyl, 1,2,3- or 1,2,4-triazolyl, 1H- or 2H-tetrazolyl, 2-, 3- or 4-pyridyl, 2-, 4- or 5-pyrimidyl, 3- or 4-pyridazinyl, quinolyl, isoquinolyl, indolyl, etc., (25) C1-10 haloalkyl such as difluoromethyl, trifluoromethyl, trifluoroethyl, trichloroethyl, etc., (26) hydroxyimino, or (27) alkyloxyimino such as methyloxyimino, ethyloxyimino, etc.

The "hydrocarbon group which may have substituent(s)" may have 1-5 of substituent(s) selected from the above (1) to (27) and, when the "hydrocarbon group" is cycloalkyl, cycloalkenyl, aryl or aralkyl, it may have 1 to 4 of lower alkyl(s) having 1-4 carbon atoms such as methyl, ethyl, propyl, isopropyl, butyl, etc. as substituent(s), and also when it has more than one substituents, the substituents may be the same or different.

The protective group of amino in the "amino which may be protected" as a "protective group" in the acidic group which may be protected by a protective group includes, for example, the "hydrocarbon which may have substituent(s)" as defined hereinbefore.

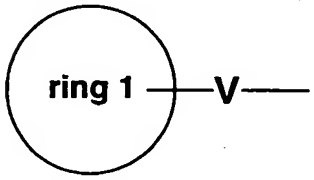
The "C1-6 alkoxy" as the protective group in the acidic group which may be protected by protective group(s) includes, for example, methoxy, ethoxy, propoxy, butoxy, pentyloxy,

hexyloxy, etc.

The "acidic group which may be protected" represented by R^1 and R^2 includes, for example, ester group such as methoxycarbonyl, ethoxycarbonyl, etc., amide group such as carbamoyl, etc.

In the present specification, the "spacer consisting of 1-8 of atom in the main chain" represented by D and E means an interval of 1-8 of atom in succession. Here the "atom in the main chain" is counted so as to minimize the atom in the main chain. Here the "spacer consisting of 1-8 of atom in the main chain" includes, for example, a divalent radical consisting of 1-8 member(s) selected from $-CH_2-$ which may have 1-2 substituent(s), -CH=CH- which may have 1-2 substituent(s), -C=C-, -NH- which may have a substituent, -CO-, -O-, -S-, -SO-, $-SO_2-$. Here the substituent of the methylene and the nitrogen atom has the same meaning as the "substituent" in the cyclic ring which may have a substituent represented by the above A, concretely, e.g. $-CR^{101}R^{102}-$, $-(CR^{101}R^{102})_2-$, $-(CR^{101}R^{102})_3-$, $-(CR^{101}R^{102})_4-$, $-CO(CR^{101}R^{102})_2-$, $-CO(CR^{101}R^{102})_3-$, $-CO(CR^{101}R^{102})_4-$, $-NR^{103}-$, -CO-, -O-, -S-, $-NR^{103}CO-$, $-CONR^{103}-$, $-NR^{103}COCR^{101}R^{102}-$, $-CONR^{103}CR^{101}R^{102}-$, $-C(R^{101})=C(R^{102})-$, -C=C- (wherein R^{101} to R^{103} are, hydrogen atom or a substituent having the same meaning as the "substituent" in the cyclic group which may have substituent represented by the above A.), etc.

In the present specification, the "substituent" represented by R^3 includes, for example, (1) alkyl which may have substituent(s), (2) alkenyl which may have substituent(s), (3) alkynyl which may have substituent(s), (4) carbocyclic ring which may have substituent(s), (5) heterocyclic ring which may have substituent(s), (6) hydroxy which may be protected, (7) thiol which may be protected, (8) amino which may be protected, (9) carbamoyl which may have substituent(s), (10) sulfamoyl which may have substituent(s), (11) carboxy, (12) alkoxycarbonyl (e.g. C1-6 alkoxycarbonyl such as methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl, etc.), (13) sulfo ($-SO_3H$), (14) sulfino, (15) phosphono, (16) nitro, (17) cyano, (18) amidino, (19) imino, (20) $-B(OH)_2$, (21) halogen (e.g. fluorine chlorine, bromine, iodine, etc.), (22) alkylsulfinyl (e.g. C1-4 alkylsulfinyl such as methylsulfinyl, ethylsulfinyl, etc.), (23) aromatic ring-sulfinyl (e.g. C6-10 aromatic ring-sulfinyl such as phenylsulfinyl), (24) alkylsulfonyl (e.g. C1-4 alkylsulfonyl such as methylsulfonyl, ethylsulfonyl, etc.), (25) aromatic ring-sulfonyl (e.g. C6-10 aromatic ring-sulfonyl such as phenylsulfonyl etc.), (26) acyl (e.g., C1-6 alkanoyl such as formyl, acetyl, propanoyl, pivaloyl etc., C6-10 aromatic ring-carbonyl such as benzoyl etc.), (27) oxo, (28) thioxo, (29) (C1-6 alkoxyimino)methyl (e.g. (methoxyimino)methyl etc.), (30)



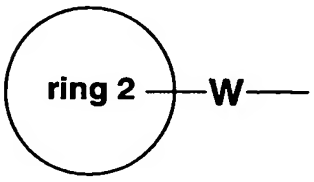
(wherein, ring 1 is a cyclic group which may have substituent(s), and V is a bond or a spacer

consisting of 1-8 of atom in the main chain.), etc.

As the "substituent" represented by R^3, (1) alkyl which may have substituent(s), (2) alkenyl which may have substituent(s), (3) alkynyl which may have substituent(s), (4) carbocyclic ring which may have substituent(s), (5) heterocyclic ring which may have substituent(s), (6) hydroxy which may be protected, (7) thiol which may be protected, (8) amino which may be protected, (9) carbamoyl which may have substituent(s), and (10) sulfamoyl which may have substituent(s) have the same meaning as those in the "substituent" in the cyclic group which may have substituent(s) represented by the above A.

In the present specification, the "cyclic group" in the cyclic group which may have substituent(s) represented by ring 1 has the same meaning as the cyclic group in the above described "cyclic group which may have substituent(s) represented by A".

In the present specification, the "substituent" in the cyclic group which may have substituent(s) represented by ring 1 includes, for example, (1) alkyl which may have substituent(s), (2) alkenyl which may have substituent(s), (3) alkynyl which may have substituent(s), (4) carbocyclic ring which may have substituent(s), (5) heterocyclic ring which may have substituent(s), (6) hydroxy which may be protected, (7) thiol which may be protected, (8) amino which may be protected, (9) carbamoyl which may have substituent(s), (10) sulfamoyl which may have substituent(s), (11) carboxy, (12) alkoxycarbonyl (e.g. C1-6 alkoxycarbonyl such as methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl, etc.), (13) sulfo ($-SO_3H$), (14) sulfino, (15) phosphono, (16) nitro, (17) cyano, (18) amidino, (19) imino, (20) $-B(OH)_2$, (21) halogen atom (e.g. fluorine, chlorine, bromine, iodine, etc.), (22) alkylsulfinyl (e.g. C1-4 alkylsulfinyl such as methylsulfinyl, ethylsulfinyl, etc.), (23) aromatic ring-sulfinyl (e.g. C6-10 aromatic ring-sulfinyl such as phenylsulfinyl), (24) alkylsulfonyl (e.g. C1-4 alkylsulfonyl such as methylsulfonyl, ethylsulfonyl, etc.), (25) aromatic ring-sulfonyl (e.g. C6-10 aromatic ring-sulfonyl such as phenylsulfonyl), (26) acyl (e.g., C1-6 alkanoyl such as formyl, acetyl, propanoyl, pivaloyl etc., C6-10 aromatic ring-carbonyl such as benzoyl etc.), (27) oxo, (28) thioxo, (29) (C1-6 alkoxyimino)methyl (e.g. (methoxyimino)methyl etc.), (30)



(wherein ring2 is a cyclic group which may have substituent(s), W is a bond or a spacer consisting of 1-8 of atom in the main chain.), etc., and 1-5 of these substituents may be positioned where acceptable.

In the present specification, as the "substituent" in the cyclic group which may have substituent(s) represented by ring 1, (1) alkyl which may have substituent(s), (2) alkenyl which

may have substituent(s), (3) alkynyl which may have substituent(s), (4) carbocyclic ring which may have substituent(s), (5) heterocyclic ring which may have substituent(s), (6) hydroxy which may be protected, (7) thiol which may be protected, (8) amino which may be protected, (9) carbamoyl which may have substituent(s), and (10) sulfamoyl which may have substituent(s) have the same meaning as those of the "substituent" in the cyclic group which may have substituent(s) represented by the above A.

In the present specification, the "cyclic group" in the cyclic group which may have substituent(s) represented by ring 2, has the same meaning as the cyclic group in the above "cyclic group optionally having substituent(s) represented by A".

In the present specification, the "substituent" in the cyclic group which may have substituent(s) represented by ring2 has the same meaning as the substituent in the above "cyclic group which may have substituent(s) represented by A".

In the present specification, the "spacer consisting of 1-8 atom(s) in the main chain" represented by V has the same meaning as the "spacer consisting of 1-8 atom(s) in the main chain" represented by the above D and E.

In the present specification, the "spacer consisting of 1-8 atom(s) in the main chain" represented by W has the same meaning as the "spacer consisting of 1-8 atom(s) in the main chain" represented by the above D and E.

The ring A is preferably a C3-15 mono-cyclic aromatic carbocyclic ring or partially or completely saturated one thereof, or a 3-15 membered mono-cyclic aromatic heterocyclic ring comprising 1-5 heteroatom(s) selected from oxygen, nitrogen and/or sulfur which may be partially or completely saturated, and more preferably a C3-8 mono-cyclic aromatic carbocyclic ring, or partially or completely saturated one thereof, and further preferably, cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclooctane, cyclopentene, cyclohexene, cycloheptene, cyclooctene, cyclopentadiene, cyclohexadiene, cycloheptadiene, cyclooctadiene, or benzene ring.

The ring B is preferably a C3-15 mono-cyclic aromatic carbocyclic ring, partially or completely saturated one thereof, or a 3-15 membered mono-cyclic aromatic heteroring comprising 1-5 of hetero atom selected from oxygen, nitrogen and/or sulfur which may be partially or completely saturated, more preferably, a 3-8 membered mono-cyclic aromatic heteroring comprising 1-3 of hetero atom selected from oxygen, nitrogen and/or sulfur which may be partially or completely saturated, furthermore preferably, pyrrole, imidazole, triazole, tetrazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, azepine, diazepine, furan, pyran, oxepin, thiophene, thiopyran, thiepin, oxazole, isoxazole, thiazole, isothiazole, furazane, oxadiazole, oxazine, oxadiazine, oxazepine, oxadiazepine, thiadiazole, thiazine, thiadiazine, thiazepine, thiadiazepine, aziridine, azetidine, pyrroline, pyrrolidine, imidazoline, imidazolidine,

triazoline, triazolidine, tetrazoline, tetrazolidine, pyrazoline, pyrazolidine, dihydropyridine, tetrahydropyridine, piperidine, dihydropyrazine, tetrahydropyrazine, piperazine, dihydropyrimidine, tetrahydropyrimidine, perhydropyrimidine, dihydropyridazine, tetrahydropyridazine, perhydropyridazine, dihydroazepine, tetrahydroazepine, perhydroazepine, dihydrodiazepine, tetrahydrodiazepine, perhydrodiazepine, oxirane, oxetane, dihydrofuran, tetrahydrofuran, dihydropyran, tetrahydropyran, dihydrooxepin, tetrahydrooxepin, perhydrooxepin, thiiran, thietane, dihydrothiophene, tetrahydrothiophene, dihydrothiopyran, tetrahydrothiopyran, dihydrothiepin, tetrahydrothiepin, perhydrothiepin, dihydrooxazole, tetrahydrooxazole (oxazolidine), dihydroisoxazole, tetrahydroisoxazole(isoxazolidine), dihydrothiazole, tetrahydrothiazole (thiazolidine), dihydroisothiazole, tetrahydroisothiazole (isothiazolidine), dihydrofurazane, tetrahydrofurazane, dihydrooxadiazole, tetrahydrooxadiazole (oxadiazolidine), dihydrooxazine, tetrahydrooxazine, dihydrooxadiazine, tetrahydrooxadiazine, dihydrooxazepine, tetrahydrooxazepine, perhydrooxazepine, dihydrooxadiazepine, tetrahydrooxadiazepine, perhydrooxadiazepine, dihydrothiadiazole, tetrahydrothiadiazole (thiadiazolidine), dihydrothiazine, tetrahydrothiazine, dihydrothiadiazine, tetrahydrothiadiazine, dihydrothiazepine, tetrahydrothiazepine, perhydrothiazepine, dihydrothiadiazepine, tetrahydrothiadiazepine, perhydrothiadiazepine, morpholine, thiomorpholine, oxathiane, dioxolane, dioxane, dithiolane or dithiane ring.

Y is preferably a carbon atom.

Z is preferably a carbon atom.

is preferably a double bond.

R^1 is preferably carboxy, acylsulfonamide, triazolylsulfynyl, triazolylsulfonyl, hydroxyisothiazolyl, hydroxythiadiazolyl or tetrazolyl, more preferably carboxy, acylsulfonamide or tetrazolyl.

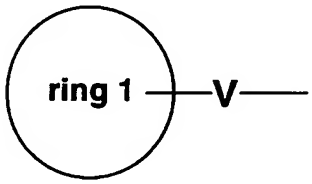
R^2 is preferably carboxy, acylsulfonamide, triazolylsulfynyl, triazolylsulfonyl, hydroxyisothiazolyl, hydroxythiadiazolyl or tetrazolyl, more preferably carboxy, acylsulfonamide or tetrazolyl.

D is preferably a bond or a spacer consisting of 1-5 of atom in the main chain, more preferably, a divalent radical consisting of a combination of 1-5 member(s) selected from a bond, methylene ($-CH_2-$) which may have 1-2 substituent(s), nitrogen atom (-NH-) which may have a substituent, -CO-, -O-, -S-, -SO- and $-SO_2-$, furthermore preferably, a bond, $-CO-(CH_2)_2-$, $-CO-(CH_2)_3-$, $-CO-(CH_2)_4-$, or $-(CH_2)_3-$.

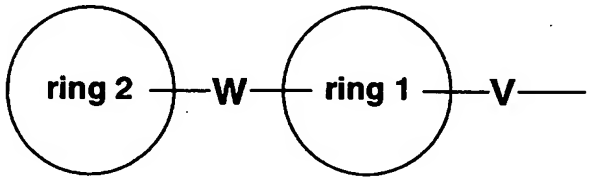
E is preferably a bond or a spacer consisting of 1-5 of atom in the main chain, more preferably, a divalent radical consisting of 1-5 members selected from a bond, methylene ($-CH_2-$) which may have 1-2 of substituent(s), nitrogen atom (-NH-) which may have a substituent, -CO-, -O-,

-S-, -SO- and $-SO_2-$, furthermore preferably, a bond, $-CO-(CH_2)_2-$, $-CO-(CH_2)_3-$, $-CO-(CH_2)_4-$, or $-(CH_2)_3-$.

R^3 is preferably,

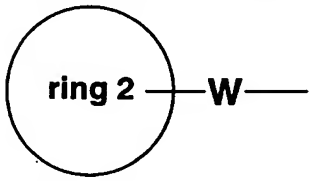


(wherein all symbols have the same meaning as described hereinbefore), more preferably,

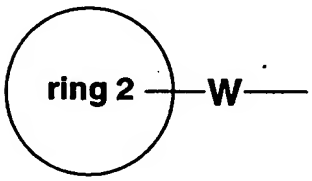


(wherein all symbols have the same meaning as described hereinbefore).

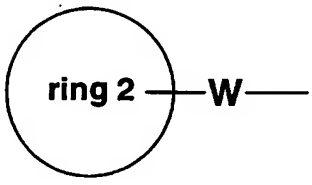
The substituent of ring 1 is preferably,



(wherein all symbols have the same meaning as described hereinbefore), or C1-20 straight or branched alkyl, alkenyl or alkynyl in which optional 1-3 carbon atom(s) may be replaced by oxygen, sulfur, halogen, nitrogen, benzene ring, thiophene ring, C4-7 carbocyclic ring, carbonyl, carbonyloxy, hydroxyl, carboxy, azido, nitro, and more preferably,

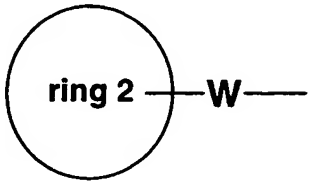


(wherein all symbols have the same meaning as described hereinbefore), or C1-10 straight or branched alkyl, alkenyl or alkynyl in which optional 1-2 of the carbon atom(s) may be replaced by oxygen, sulfur, benzene ring, thiophene or C4-7 carbocyclic ring, hydroxy and more preferably,



(wherein all symbols have the same meaning as described hereinbefore), or C1-10 straight or branched alkyl, alkenyl or alkynyl in which optional 1-2 of the carbon atom(s) may be replaced

by oxygen, benzene ring, C5-7 carbocyclic ring, and most preferably,



(wherein all symbols have the same meaning as described hereinbefore), n-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl, n-butyloxy, n-pentyloxy, n-hexyloxy, n-heptyloxy, n-octyloxy, n-nonyloxy, (2E)-2-pentenyloxy, (2E)-2-hexenyloxy, (2E)-2-heptenyloxy, (2E)-2-octenyloxy, (2E)-2-nonenyloxy, 7-octenyloxy, 2-octynyloxy, (2E)-2,7-octadienyloxy, 2-phenylethoxy, 3-phenylpropoxy, 4-phenylbutoxy or 5-phenylpentyloxy.

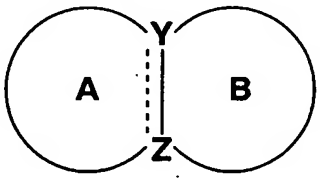
The ring 1 is preferably, C3-15 carbocyclic ring, or 3-15 membered mono-, bi- or tri-cyclic partially or completely saturated aromatic heterocyclic ring comprising 1-5 of hetero atom selected from oxygen, nitrogen and/or sulfur, and more preferably C3-15 mono-, bi- or tri-cyclic aromatic carbocyclic ring, partly or completely saturated one thereof, spiro bi-cyclic carbocyclic ring and bridged carbocyclic ring, e.g. cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclooctane, cyclononane, cyclodecane, cycloundecane, cyclododecane, cyclotridecane, cyclotetradecane, cyclopentadecane, cyclopentene, cyclohexene, cycloheptene, cyclooctene, cyclopentadiene, cyclohexadiene, cycloheptadiene, cyclooctadiene, benzene, pentalene, perhydropentalene, azulene, perhydroazulene, indene, perhydroindene, indan, naphthalene, dihydronaphthalene, tetrahydronaphthalene, perhydronaphthalene, heptalene, perhydroheptalene, biphenylene, as-indacene, s-indacene, acenaphthylene, acenaphthene, fluorene, phenalene, phenanthrene, anthracene, spiro[4.4]nonane, spiro[4.5]decane, spiro[5.5]undecane, bicyclo[2.2.1]heptane, bicyclo[2.2.1]hept-2-ene, bicyclo[3.1.1]heptane, bicyclo[3.1.1]hept-2-ene, bicyclo[2.2.2]octane, bicyclo[2.2.2]oct-2-ene, adamantane or noradamantane ring, etc.

The ring 2 is preferably, C3-15 carbocyclic ring, or 3-15 membered mono-, bi- or tri-cyclic partially or completely saturated aromatic heterocyclic ring comprising 1-5 of hetero atom selected from oxygen, nitrogen and/or sulfur, and more preferably C3-15 mono-, bi- or tri-cyclic aromatic carbocyclic ring, partly or completely saturated one thereof, spiro bi-cyclic carbocyclic ring and bridged carbocyclic ring, e.g. cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclooctane, cyclononane, cyclodecane, cycloundecane, cyclododecane, cyclotridecane, cyclotetradecane, cyclopentadecane, cyclopentene, cyclohexene, cycloheptene, cyclooctene, cyclopentadiene, cyclohexadiene, cycloheptadiene, cyclooctadiene, benzene, pentalene, perhydropentalene, azulene, perhydroazulene, indene, perhydroindene, indan, naphthalene, dihydronaphthalene, tetrahydronaphthalene, perhydronaphthalene, heptalene, perhydroheptalene, biphenylene, as-indacene, s-indacene, acenaphthylene, acenaphthene,

fluorene, phenalene, phenanthrene, anthracene, spiro[4.4]nonane, spiro[4.5]decane, spiro[5.5]undecane, bicyclo[2.2.1]heptane, bicyclo[2.2.1]hept-2-ene, bicyclo[3.1.1]heptane, bicyclo[3.1.1]hept-2-ene, bicyclo[2.2.2]octane, bicyclo[2.2.2]oct-2-ene, adamantane or noradamantane ring, etc.

V is preferably, a bond or a spacer consisting of 1-5 of atom in the main chain, more preferably, a bond, a divalent radical consisting of 1-5 member(s) selected from methlene ($-CH_2-$) optionally having 1-2 substituent(s), nitrogen atom (-NH-) optionally having a substituent, -CO-, -O-, -S-, -SO- and SO_2-, moreover preferably, -NHCO-, $-NR^{103}CO-$, -CONH-, $-CONR^{103}-$, $-NR^{103}COCR^{101}R^{102}-$, $-CONR^{103}CR^{101}R^{102}-$, $-O-CH_2-$, $-CH_2O-$, (wherein, R^{101} to R^{103} are hydrogen or have the same meanings as the "substituent" in the cyclic group which may have substituent(s) represented by the above A).

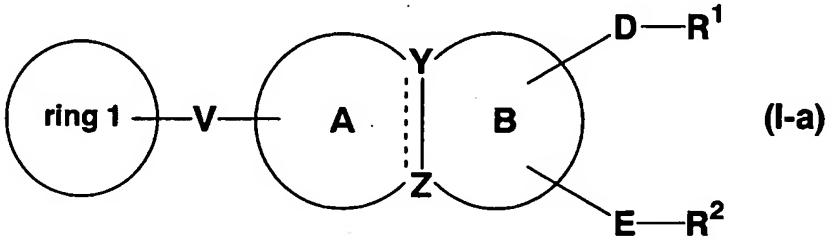
W is preferably, a bond or a spacer consisting of 1-6 of atom in the main chain, more preferably, a divalent radical consisting of 1-6 member(s) selected from a bond, methylene ($-CH_2-$) optionally having 1-2 substituent(s), nitrogen atom (-NH-) optionally having a substituent, -CO-, -O-, -S-, -SO-, $-SO_2-$, further preferably, $-O-(CH_2)_2-$, $-O-(CH_2)_3-$, $-O-(CH_2)_4-$, $-O-(CH_2)_5-$, $-CH_2-O-$, $-(CH_2)_2-O-$, $-(CH_2)_3-O-$, $-(CH_2)_4-O-$, $-(CH_2)_5-O-$, $-O-(CH_2)_3-O-$, $-O-(CH_2)_4-O-$, or $-O-(CH_2)_5-O-$.



is preferably, 3,4-dihydro-2H-1,4-benzoxazine, chroman, 2,3-dihydro-1,4-benzoxathiin, 2,3-dihydro-1,4-benzodioxin, 3,4-dihydro-2H-1,4-benzothiazine, thiochroman, 2,3-dihydro-1,4-benzodithiine, 1,2,3,4-tetrahydroquinoxaline, 1,2,3,4-tetrahydroquinoline, 1,2,3,4-tetrahydronaphthalene, 2H-chromene, 2H-thiochromene, 1,2-dihydroquinoline, 1,2-dihydronaphthalene, 4H-1,4-benzoxazine, 4H-chromene, 1,4-benzoxathiin, 1,4-benzodioxin, 4H-1,4-benzothiazine, 4H-thiochromene, 1,4-benzodithiin, 1,5-naphthyridine, 1,8-naphthyridine, 2,7-naphthyridine, 1,4-dihydronaphthalene, naphthalene, quinoline, isoquinoline, quinoxaline, 1,2,3,4-tetrahydroisoquinoline, 3,4-dihydro-1H-isochromene, 3,4-dihydro-1H-isothiochromene, cinnoline, phthalazine, 4H-chromen-4-one, 4(1H)-quinolinone, 4H-thiochromen-4-one, 3,4-dihydro-2(1H)-quinolinone, 2(1H)-quinolinone, 2H-chromen-2-one, indan, indoline, 2,3-dihydro-1-benzofuran, 1H-indole, 1-benzofuran, 1-benzothiophene, 1H-indazole, 1,2-benzisoxazole, 1,2-benzisothiazole, 1H-benzimidazole, 1,3-benzoxazole or 1,3-benzothiazole ring and more preferably, 3,4-dihydro-2H-1,4-benzoxazine, chroman, 2,3-dihydro-1,4-benzoxathiin, 2,3-dihydro-1,4-benzodioxin, 3,4-dihydro-2H-1,4-benzothiazine, thiochroman, 2,3-dihydro-1,4-benzodithiin, 1,2,3,4-tetrahydroquinoxaline,

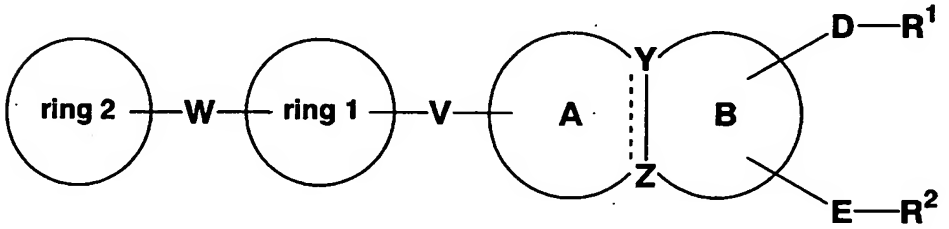
1,2,3,4-tetrahydroquinoline, 1,2,3,4-tetrahydronaphthalene, 2H-chromene, 2H-thiochromene, 1,2-dihydroquinoline, 1,2-dihydronaphthalene, 4H-1,4-benzoxazine, 4H-chromene, 1,4-benzoxathiin, 1,4-benzodioxin, 4H-1,4-benzothiazine, 4H-thiochromene, 1,4-benzodithiin, 1,4-dihydronaphthalene, naphthalene, quinoline, isoquinoline, quinoxaline, 1,2,3,4-tetrahydroisoquinoline, 3,4-dihydro-1H-isochromene, 3,4-dihydro-1H-isothiochromene, cinnoline, phthalazine, 4H-chromen-4-one, 4(1H)-quinolinone, 4H-thiochromen-4-one, 3,4-dihydro-2(1H)-quinolinone, 2(1H)-quinolinone, or 2H-chromen-2-one ring, more preferably, 3,4-dihydro-2H-1,4-benzoxazine, 3,4-dihydro-2H-1,4-benzothiazine, 1,2,3,4-tetrahydroquinoxaline, 1,2,3,4-tetrahydroquinoline, 1,2-dihydroquinoline, 4H-1,4-benzoxazine, 4H-1,4-benzothiazine, quinoline, isoquinoline, quinoxaline, 1,2,3,4-tetrahydroisoquinoline, cinnoline, phthalazine, 4(1H)-quinolinone, 3,4-dihydro-2(1H)-quinolinone, or 2(1H)-quinolinone,.

Among the compounds of formula (I), preferable compounds are, the compound of formula (I-a)



(I-a)

(wherein all symbols have the same meaning as described hereinbefore), more preferably, the compound of formula (I-b)

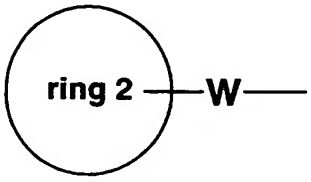


(I-b)

(wherein all symbols have the same meaning as described hereinbefore).

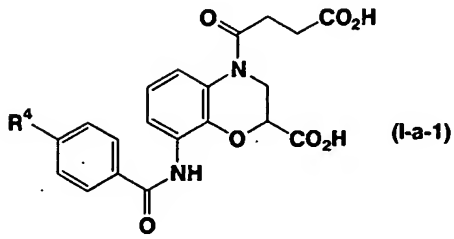
Additionally, preferable compounds in the present invention are the compounds described in tables 1 to 36 and the compounds shown in the Examples, and salts thereof, solvates thereof, or prodrugs thereof.

In the tables, R^4 is alkyl optionally having substituent(s), alkenyl optionally having substituent(s), alkynyl optionally having substituent(s), or

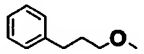
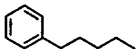
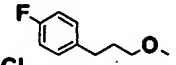
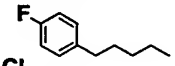
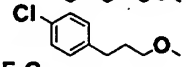
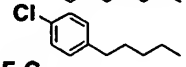
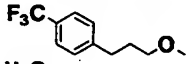
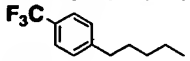
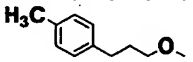
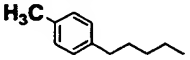
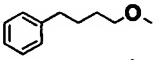
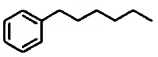
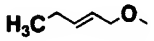
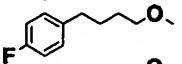
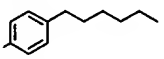
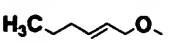
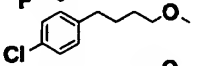
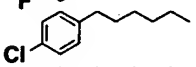
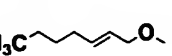
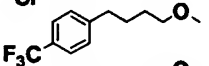
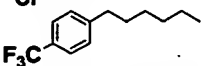
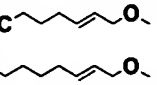
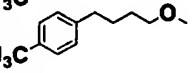
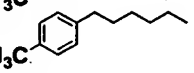
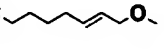
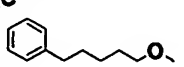
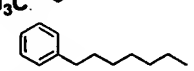
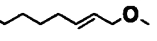
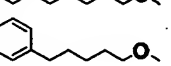
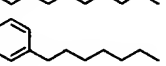
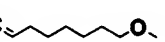
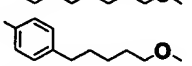
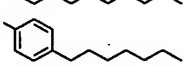
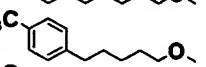
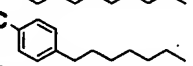
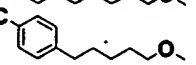
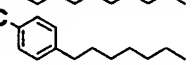


wherein all symbols have the same meaning as described hereinbefore.

Table 1



(I-a-1)

	R^4		R^4		R^4
1	*n*-C_4H_9-	22		37	
2	*n*-C_5H_{11}-				
3	*n*-C_6H_{13}-	23		38	
4	*n*-C_7H_{15}-				
5	*n*-C_8H_{17}-	24		39	
6	*n*-C_9H_{19}-				
7	*n*-C_4H_9-O-	25		40	
8	*n*-C_5H_{11}-O-				
9	*n*-C_6H_{13}-O-	26		41	
10	*n*-C_7H_{15}-O-				
11	*n*-C_8H_{17}-O-	27		42	
12	*n*-C_9H_{19}-O-				
13		28		43	
14		29		44	
15		30		45	
16		31		46	
17		32		47	
18		33		48	
19		34		49	
20		35		50	
21		36		51	

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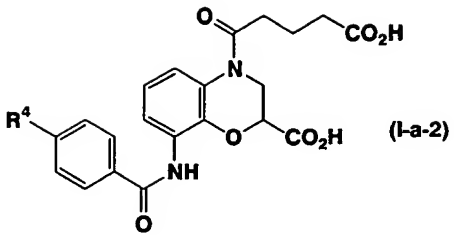
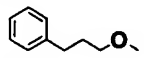
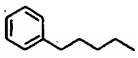
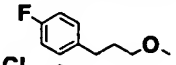
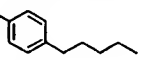
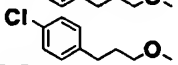
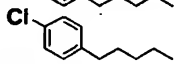
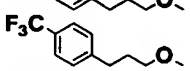
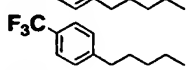
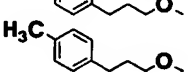
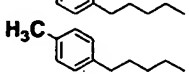


(I-a-2)

	R^4		R^4		R^4
1	*n*-C_4H_9-	22		37	
2	*n*-C_5H_{11}-	23		38	
3	*n*-C_6H_{13}-	24		39	
4	*n*-C_7H_{15}-	25		40	
5	*n*-C_8H_{17}-	26		41	
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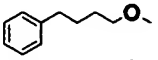
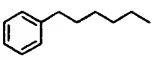
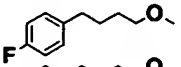
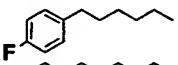
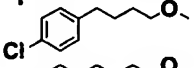
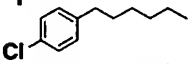
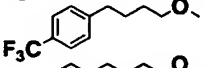
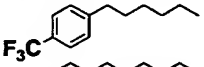
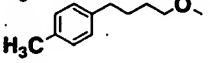
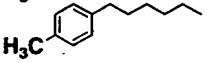
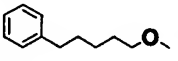
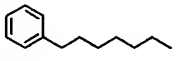
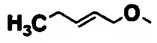
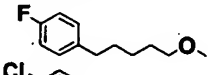
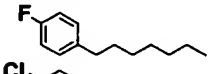
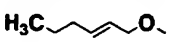
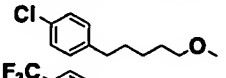
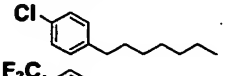
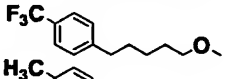
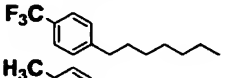
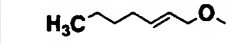
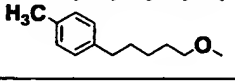
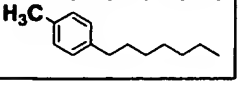
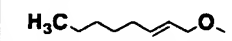
7	*n*-C_4H_9-O-	27		42	
8	*n*-C_5H_{11}-O-	28		43	
9	*n*-C_6H_{13}-O-	29		44	
10	*n*-C_7H_{15}-O-	30		45	
11	*n*-C_8H_{17}-O-	31		46	
12	*n*-C_9H_{19}-O-	32		47	
13		33		48	
14		34		49	
15		35		50	
16		36		51	
17					
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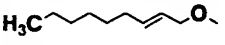
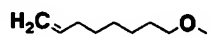
19					
20					
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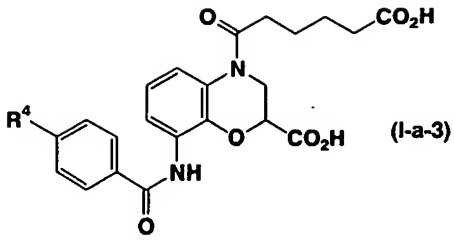
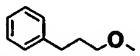
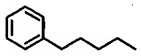
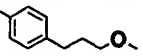
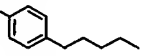
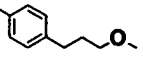
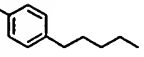
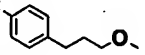
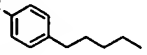
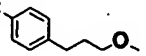
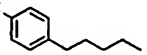
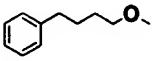
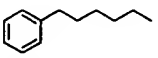
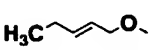
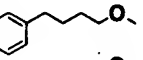
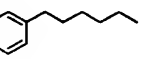
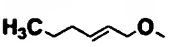
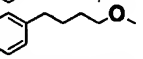
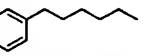
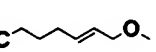
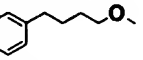
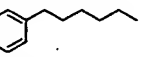
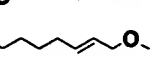
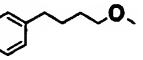
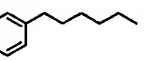
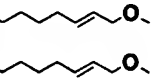
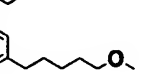
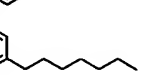
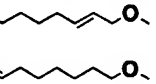
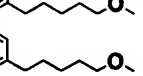
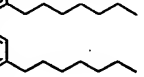
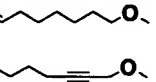
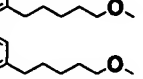
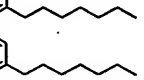
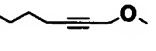
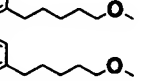
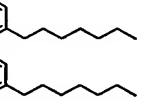
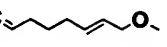
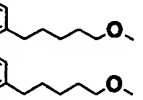
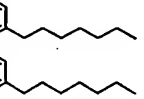


(I-a-3)

	R^4		R^4		R^4
1	*n*-C_4H_9-	22		37	
2	*n*-C_5H_{11}-				
3	*n*-C_6H_{13}-	23		38	
4	*n*-C_7H_{15}-				
5	*n*-C_8H_{17}-	24		39	
6	*n*-C_9H_{19}-				
7	*n*-C_4H_9-O-	25		40	
8	*n*-C_5H_{11}-O-				
9	*n*-C_6H_{13}-O-	26		41	
10	*n*-C_7H_{15}-O-				
11	*n*-C_8H_{17}-O-	27		42	
12	*n*-C_9H_{19}-O-				
13		28		43	
14		29		44	
15		30		45	
16		31		46	
17		32		47	
18		33		48	
19		34		49	
20		35		50	
21		36		51	

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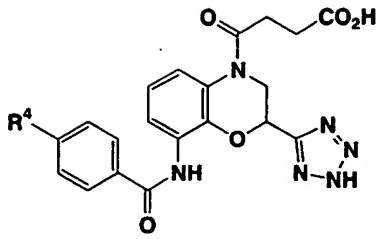
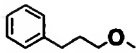
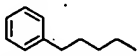
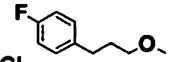
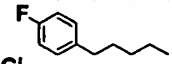
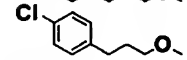
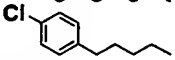
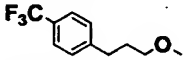
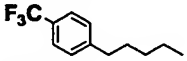
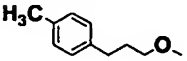
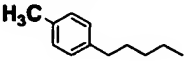
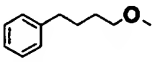
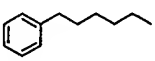
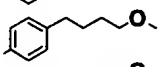
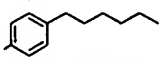
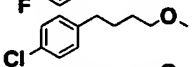
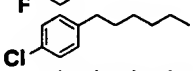
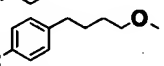
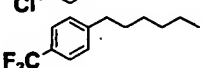
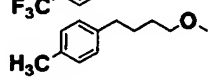
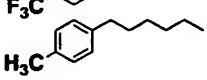
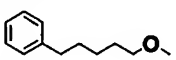
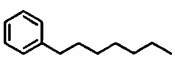
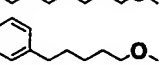
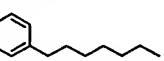
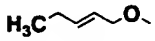
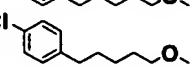
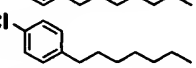
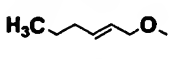
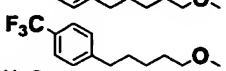
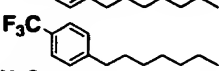
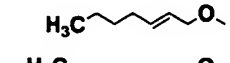
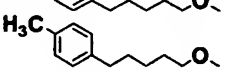
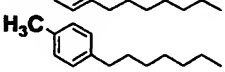


(I-a-4)

	R^4		R^4		R^4
1	*n*-C_4H_9-	22		37	
2	*n*-C_5H_{11}-	23		38	
3	*n*-C_6H_{13}-	24		39	
4	*n*-C_7H_{15}-	25		40	
5	*n*-C_8H_{17}-	26		41	
6	*n*-C_9H_{19}-	27		42	
7	*n*-C_4H_9-O-	28		43	
8	*n*-C_5H_{11}-O-	29		44	
9	*n*-C_6H_{13}-O-	30		45	
10	*n*-C_7H_{15}-O-	31		46	
11	*n*-C_8H_{17}-O-	32		47	
12	*n*-C_9H_{19}-O-	33		48	
13		34		49	
14		35		50	
15		36		51	
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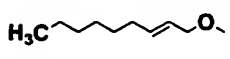
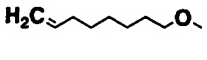
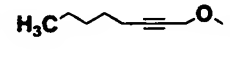
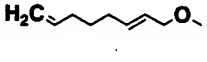
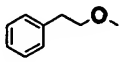
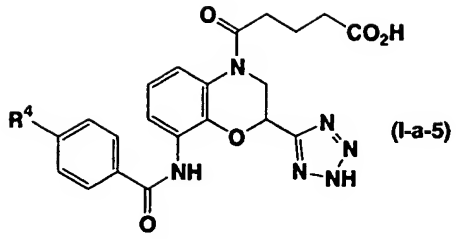
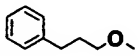
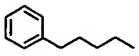
17					
18					
19					
20					
21					

Table 5



(I-a-5)

	R^4		R^4		R^4
1	*n*-C_4H_9-	22		37	
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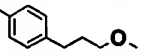
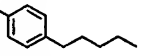
3	*n*-C_6H_{13}-	23		38	
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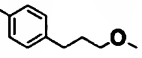
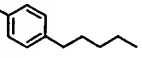
5	*n*-C_8H_{17}-	24		39	
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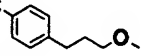
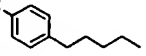
7	*n*-C_4H_9-O-	25		40	
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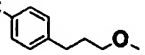
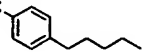
9	*n*-C_6H_{13}-O-	26		41	
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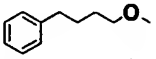
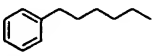
11	*n*-C_8H_{17}-O-	27		42	
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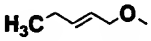
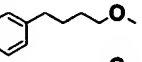
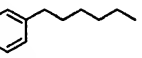
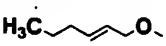
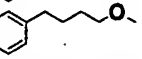
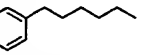
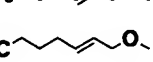
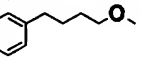
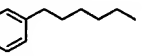
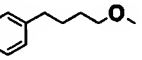
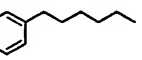
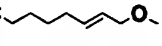
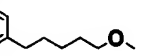
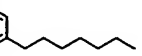
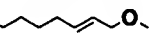
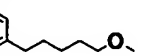
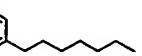
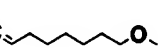
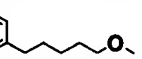
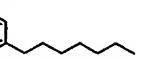
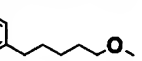
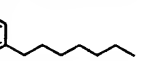
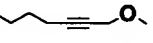
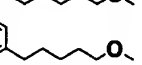
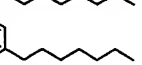
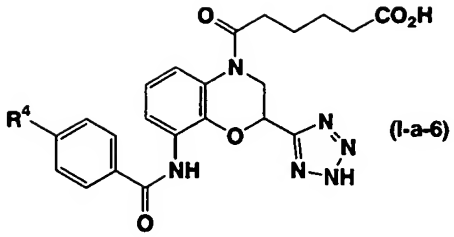
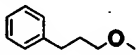
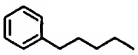
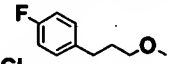
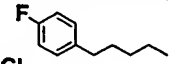
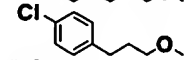
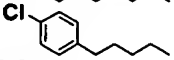
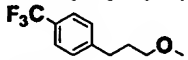
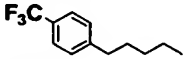
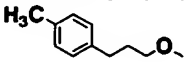
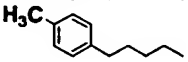
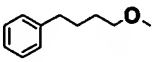
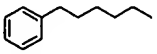
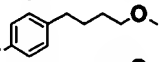
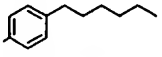
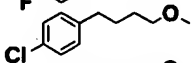
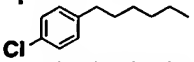
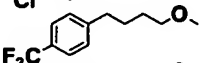
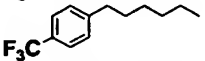
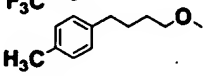
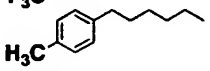
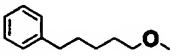
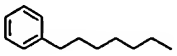
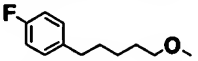
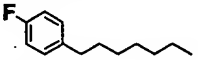
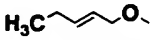
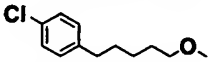
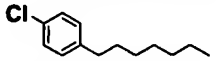
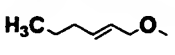
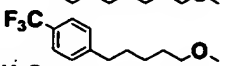
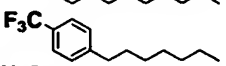
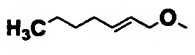
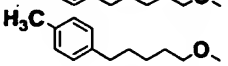
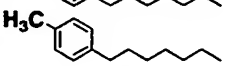
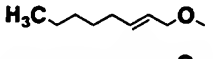
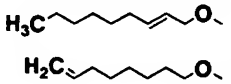
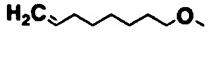
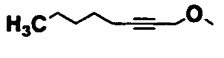
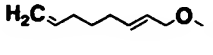
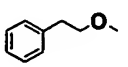
13		28		43	
14		29		44	
15		30		45	
16		31		46	
17		32		47	
18		33		48	
19		34		49	
20		35		50	
21		36		51	

Table 6



(I-a-6)

	R^4		R^4		R^4
1	*n*-C_4H_9-	22		37	
2	*n*-C_5H_{11}-	23		38	
3	*n*-C_6H_{13}-	24		39	
4	*n*-C_7H_{15}-	25		40	
5	*n*-C_8H_{17}-	26		41	
6	*n*-C_9H_{19}-	27		42	
7	*n*-C_4H_9-O-	28		43	
8	*n*-C_5H_{11}-O-	29		44	
9	*n*-C_6H_{13}-O-	30		45	
10	*n*-C_7H_{15}-O-	31		46	
11	*n*-C_8H_{17}-O-	32		47	
12	*n*-C_9H_{19}-O-	33		48	
13		34		49	
14		35		50	
15		36		51	
16					
17					
18					
19					
20					
21					

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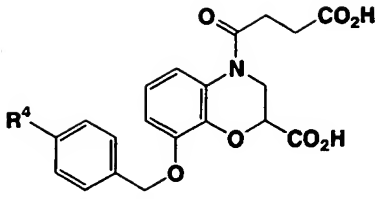
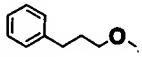
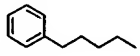
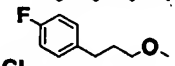
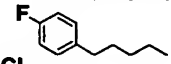
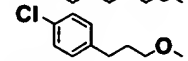
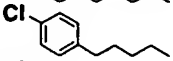
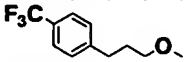
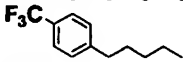
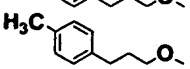
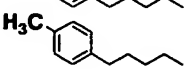
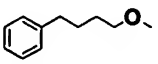
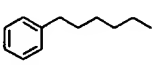
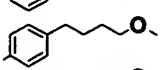
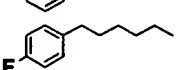
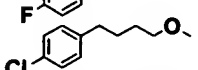
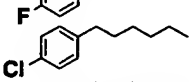
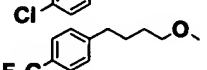
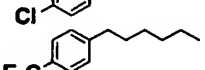
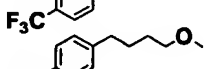
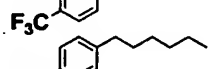
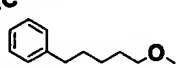
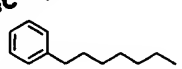
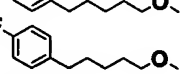
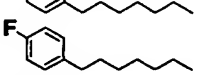
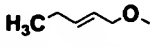
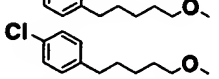
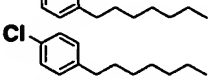
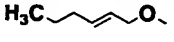
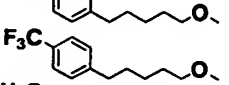
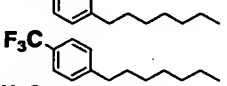
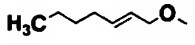
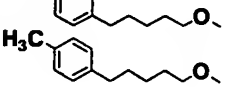
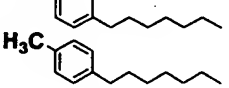
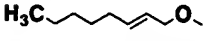
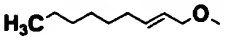
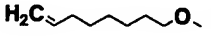
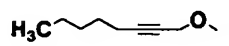
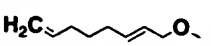
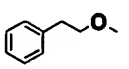


(I-a-7)

	R^4		R^4		R^4
1	*n*-C_4H_9-	22		37	
2	*n*-C_5H_{11}-	23		38	
3	*n*-C_6H_{13}-	24		39	
4	*n*-C_7H_{15}-	25		40	
5	*n*-C_8H_{17}-	26		41	
6	*n*-C_9H_{19}-	27		42	
7	*n*-C_4H_9-O-	28		43	
8	*n*-C_5H_{11}-O-	29		44	
9	*n*-C_6H_{13}-O-	30		45	
10	*n*-C_7H_{15}-O-	31		46	
11	*n*-C_8H_{17}-O-	32		47	
12	*n*-C_9H_{19}-O-	33		48	
13		34		49	
14		35		50	
15		36		51	
16					
17					
18					
19					
20					
21					

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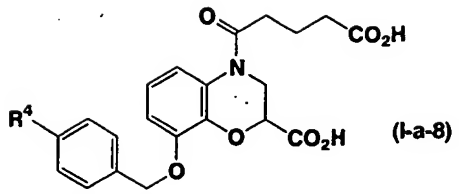
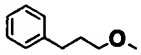
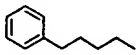
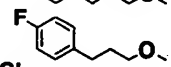
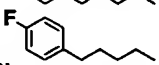
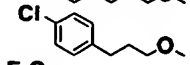
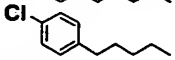
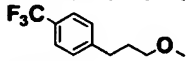
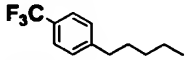
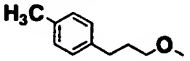
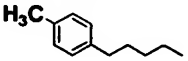
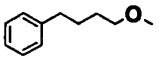
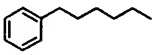


(I-a-8)

	R4		R4		R4
1	*n*-C_4H_9-	22		37	
2	*n*-C_5H_{11}-				
3	*n*-C_6H_{13}-	23		38	
4	*n*-C_7H_{15}-				
5	*n*-C_8H_{17}-	24		39	
6	*n*-C_9H_{19}-				
7	*n*-C_4H_9-O-	25		40	
8	*n*-C_5H_{11}-O-				
9	*n*-C_6H_{13}-O-	26		41	
10	*n*-C_7H_{15}-O-				
11	*n*-C_8H_{17}-O-	27		42	
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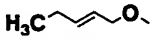
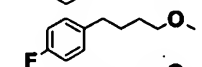
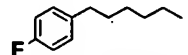
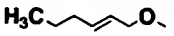
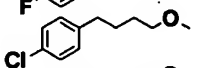
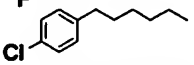
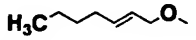
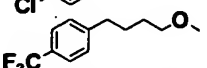
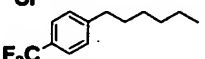
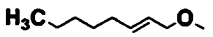
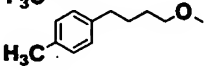
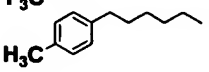
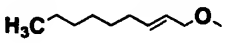
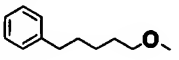
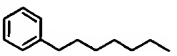
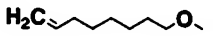
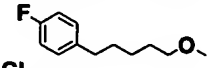
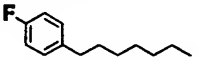
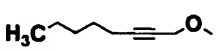
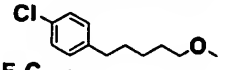
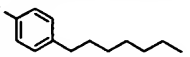
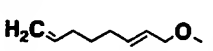
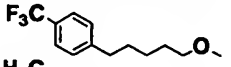
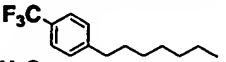
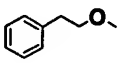
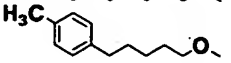
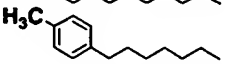
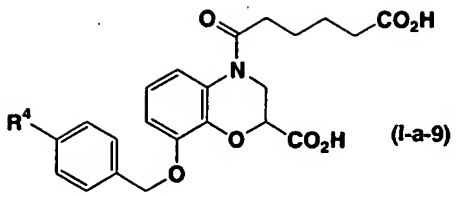
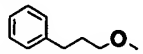
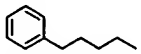
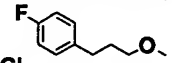
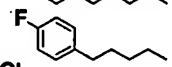
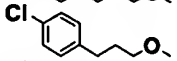
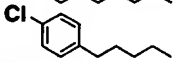
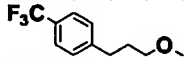
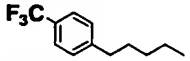
13		28		43	
14		29		44	
15		30		45	
16		31		46	
17		32		47	
18		33		48	
19		34		49	
20		35		50	
21		36		51	

Table 9



(I-a-9)

	R^4		R^4		R^4
1	*n*-C_4H_9-	22		37	
2	*n*-C_5H_{11}-				
3	*n*-C_6H_{13}-	23		38	
4	*n*-C_7H_{15}-				
5	*n*-C_8H_{17}-	24		39	
6	*n*-C_9H_{19}-				
7	*n*-C_4H_9-O-	25		40	
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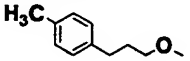
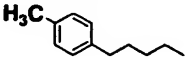
9	*n*-C_6H_{13}-O-	26		41	
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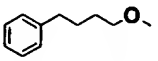
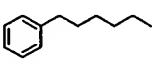
11	*n*-C_8H_{17}-O-	27		42	
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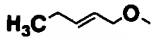
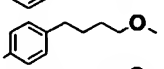
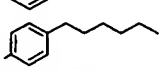
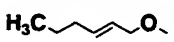
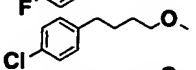
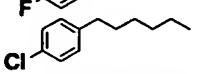
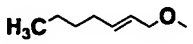
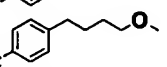
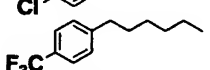
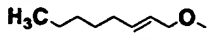
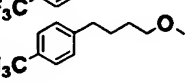
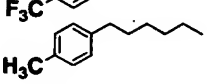
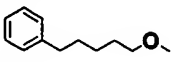
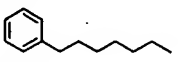
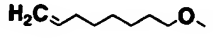
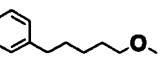
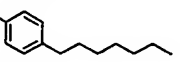
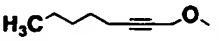
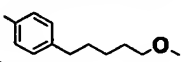
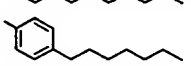
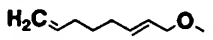
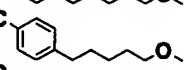
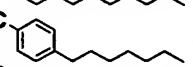
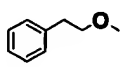
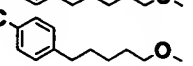
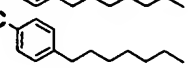
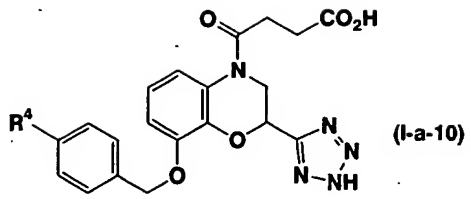
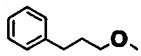
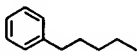
13		28		43	
14		29		44	
15		30		45	
16		31		46	
17		32		47	
18		33		48	
19		34		49	
20		35		50	
21		36		51	

Table 10



(I-a-10)

	R4		R4		R4
1	*n*-C_4H_9-	22		37	
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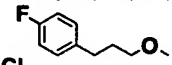
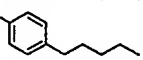
3	*n*-C_6H_{13}-	23		38	
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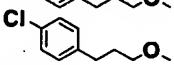
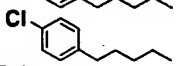
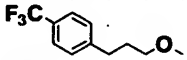
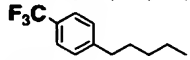
5	*n*-C_8H_{17}-	24		39	
6	*n*-C_9H_{19}-				
7	*n*-C_4H_9-O-	25		40	
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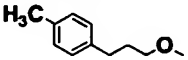
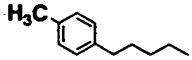
9	*n*-C_6H_{13}-O-	26		41	
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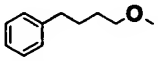
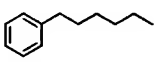
11	*n*-C_8H_{17}-O-	27		42	
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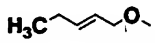
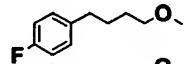
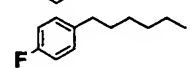
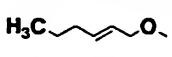
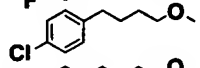
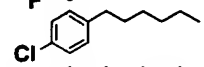
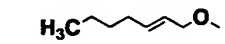
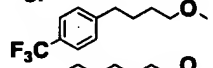
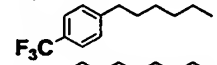
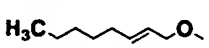
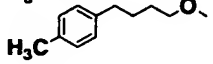
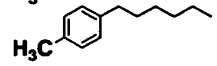
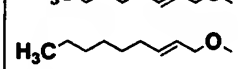
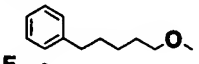
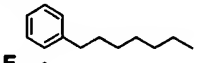
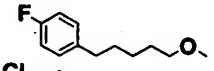
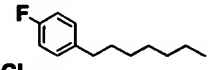
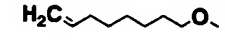
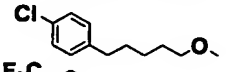
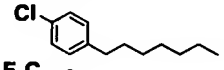
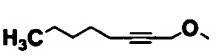
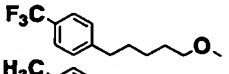
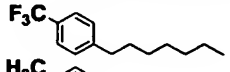
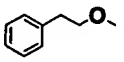
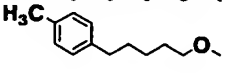
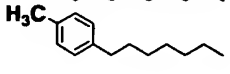
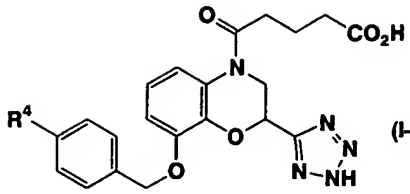
13		28		43	
14		29		44	
15		30		45	
16		31		46	
17		32		47	
18		33		48	
19		34		49	
20		35		50	
21		36		51	

Table 11



(I-a-11)

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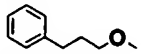
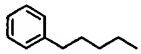
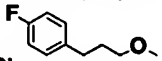
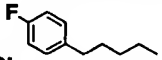
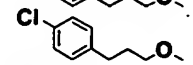
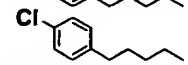
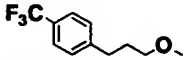
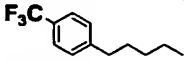
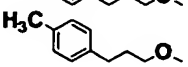
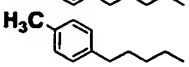
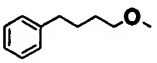
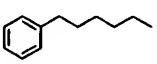
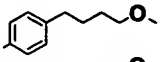
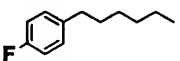
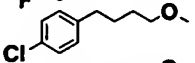
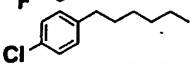
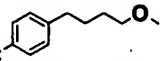
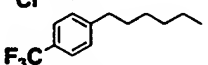
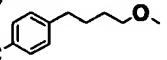
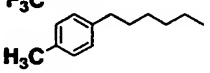
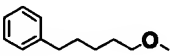
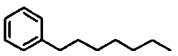
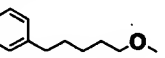
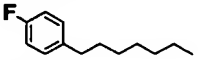
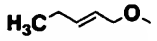
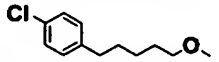
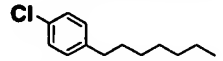
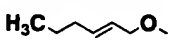
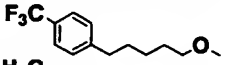
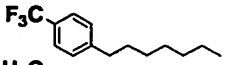
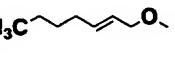
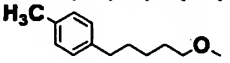
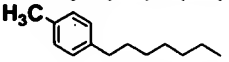
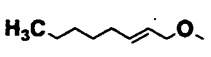
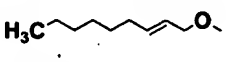
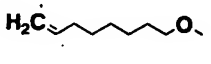
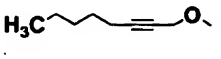
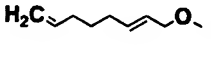
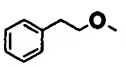
1	*n*-C_4H_9-	22		37	
2	*n*-C_5H_{11}-	23		38	
3	*n*-C_6H_{13}-	24		39	
4	*n*-C_7H_{15}-	25		40	
5	*n*-C_8H_{17}-	26		41	
6	*n*-C_9H_{19}-	27		42	
7	*n*-C_4H_9-O-	28		43	
8	*n*-C_5H_{11}-O-	29		44	
9	*n*-C_6H_{13}-O-	30		45	
10	*n*-C_7H_{15}-O-	31		46	
11	*n*-C_8H_{17}-O-	32		47	
12	*n*-C_9H_{19}-O-	33		48	
13		34		49	
14		35		50	
15		36		51	
16					
17					
18					
19					
20					
21					

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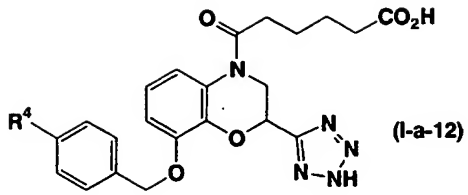


(I-a-12)

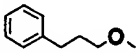
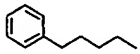
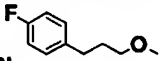
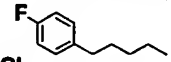
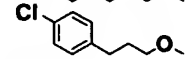
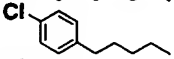
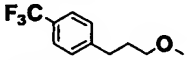
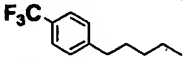
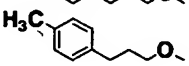
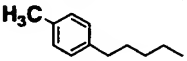
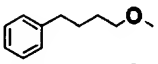
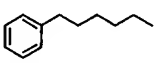
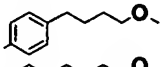
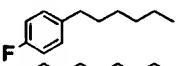
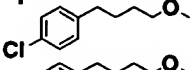
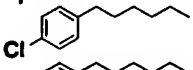
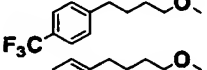
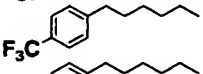
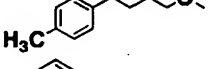
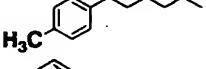
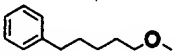
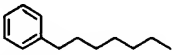
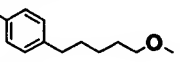
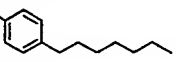
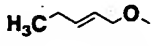
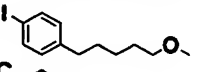
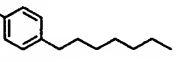
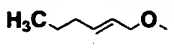
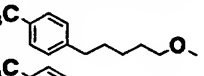
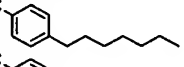
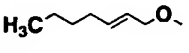
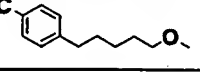
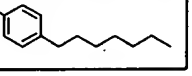
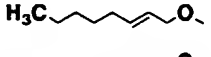
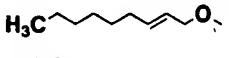
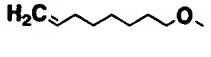
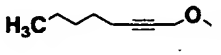
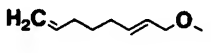
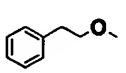
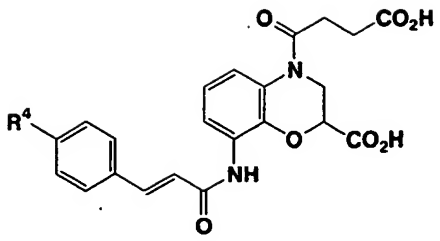
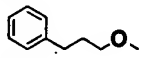
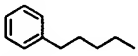
	R^4		R^4		R^4
1	*n*-C_4H_9-	22		37	
2	*n*-C_5H_{11}-	23		38	
3	*n*-C_6H_{13}-	24		39	
4	*n*-C_7H_{15}-	25		40	
5	*n*-C_8H_{17}-	26		41	
6	*n*-C_9H_{19}-	27		42	
7	*n*-C_4H_9-O-	28		43	
8	*n*-C_5H_{11}-O-	29		44	
9	*n*-C_6H_{13}-O-	30		45	
10	*n*-C_7H_{15}-O-	31		46	
11	*n*-C_8H_{17}-O-	32		47	
12	*n*-C_9H_{19}-O-	33		48	
13		34		49	
14		35		50	
15		36		51	
16					
17					
18					
19					
20					
21					

Table 13



(I-a-13)

	R^4		R^4		R^4
1	*n*-C_4H_9-	22		37	
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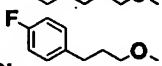
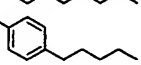
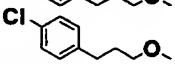
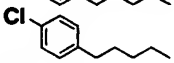
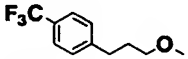
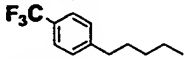
3	*n*-C_6H_{13}-	23		38	
4	*n*-C_7H_{15}-				
5	*n*-C_8H_{17}-	24		39	
6	*n*-C_9H_{19}-				
7	*n*-C_4H_9-O-	25		40	
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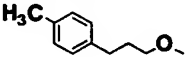
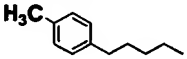
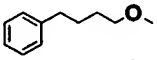
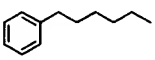
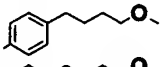
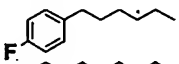
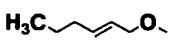
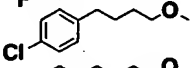
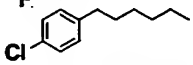
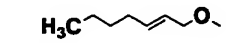
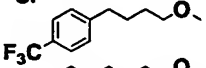
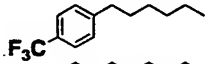
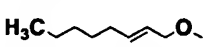
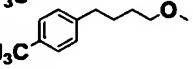
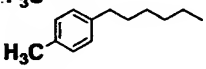
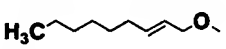
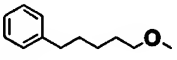
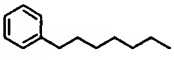
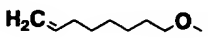
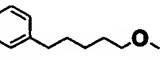
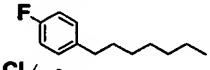
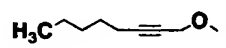
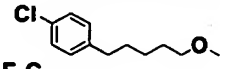
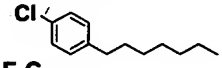
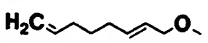
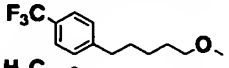
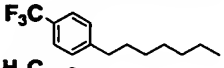
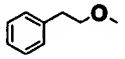
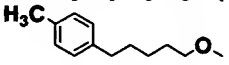
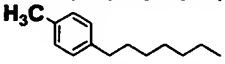
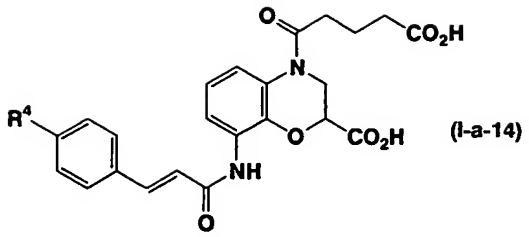
9	*n*-C_6H_{13}-O-	26		41	
10	*n*-C_7H_{15}-O-				
11	*n*-C_8H_{17}-O-	27		42	
12	*n*-C_9H_{19}-O-				
13		28		43	
14		29		44	
15		30		45	
16		31		46	
17		32		47	
18		33		48	
19		34		49	
20		35		50	
21		36		51	

Table 14



(I-a-14)

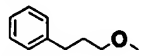
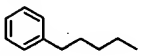
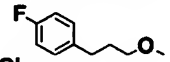
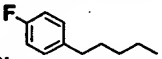
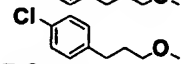
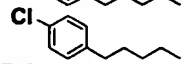
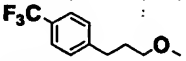
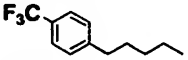
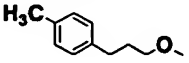
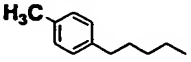
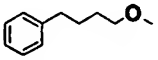
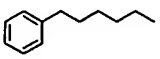
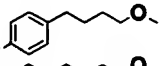
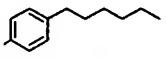
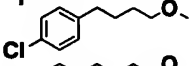
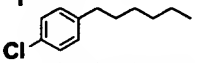
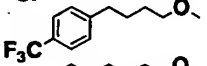
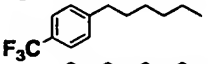
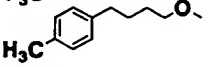
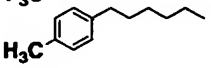
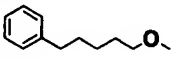
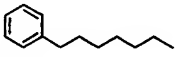
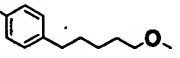
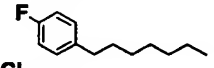
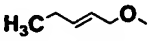
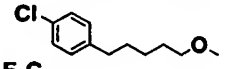
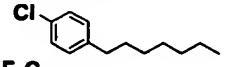
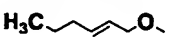
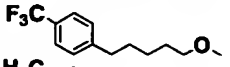
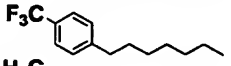
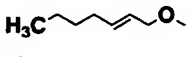
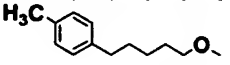
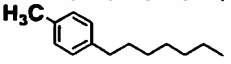
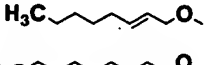
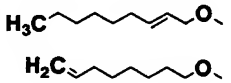
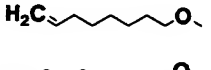
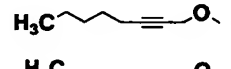
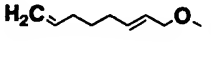
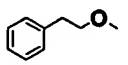
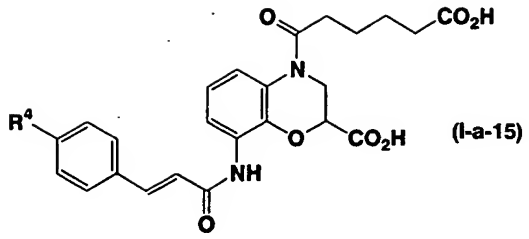
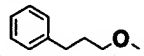
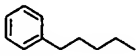
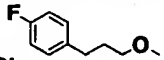
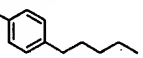
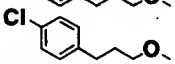
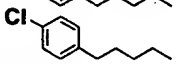
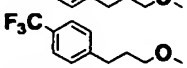
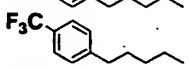
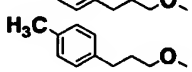
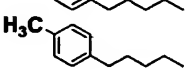
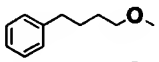
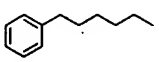
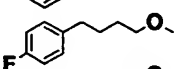
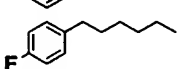
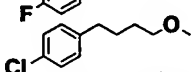
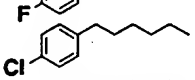
	R^4		R^4		R^4
1	*n*-C_4H_9-	22		37	
2	*n*-C_5H_{11}-	23		38	
3	*n*-C_6H_{13}-	24		39	
4	*n*-C_7H_{15}-	25		40	
5	*n*-C_8H_{17}-	26		41	
6	*n*-C_9H_{19}-	27		42	
7	*n*-C_4H_9-O-	28		43	
8	*n*-C_5H_{11}-O-	29		44	
9	*n*-C_6H_{13}-O-	30		45	
10	*n*-C_7H_{15}-O-	31		46	
11	*n*-C_8H_{17}-O-	32		47	
12	*n*-C_9H_{19}-O-	33		48	
13		34		49	
14		35		50	
15		36		51	
16					
17					
18					
19					
20					
21					

Table 15



(I-a-15)

	R^4		R^4		R^4
1	*n*-C_4H_9-	22		37	
2	*n*-C_5H_{11}-	23		38	
3	*n*-C_6H_{13}-	24		39	
4	*n*-C_7H_{15}-	25		40	
5	*n*-C_8H_{17}-	26		41	
6	*n*-C_9H_{19}-				
7	*n*-C_4H_9-O-	27		42	
8	*n*-C_5H_{11}-O-				
9	*n*-C_6H_{13}-O-	28		43	
10	*n*-C_7H_{15}-O-				
11	*n*-C_8H_{17}-O-	29		44	
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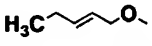
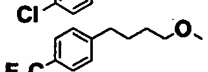
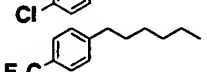
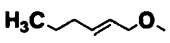
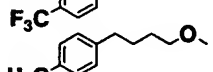
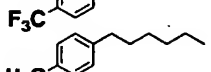
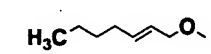
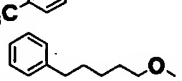
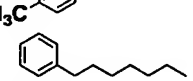
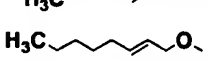
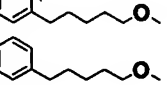
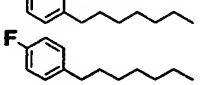
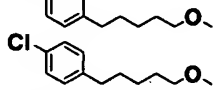
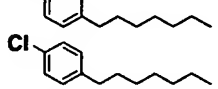
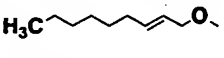
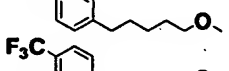
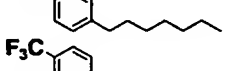
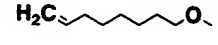
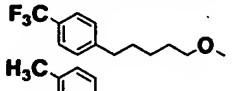
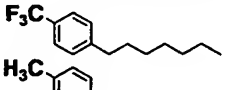
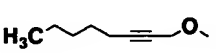
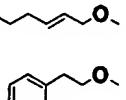
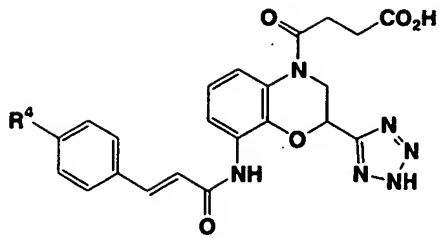
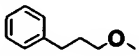
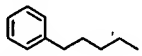
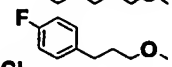
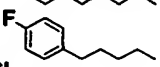
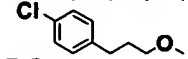
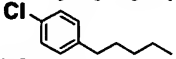
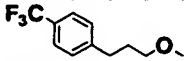
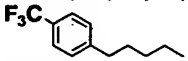
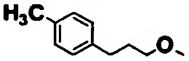
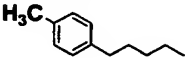
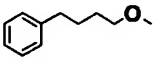
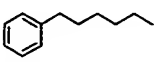
13		30		45	
14		31		46	
15		32		47	
16		33		48	
17		34		49	
18		35		50	
19		36		51	
20					
21					

Table 16



(I-a-16)

	R4		R4		R4
1	*n*-C_4H_9-	22		37	
2	*n*-C_5H_{11}-				
3	*n*-C_6H_{13}-	23		38	
4	*n*-C_7H_{15}-				
5	*n*-C_8H_{17}-	24		39	
6	*n*-C_9H_{19}-				
7	*n*-C_4H_9-O-	25		40	
8	*n*-C_5H_{11}-O-				
9	*n*-C_6H_{13}-O-	26		41	
10	*n*-C_7H_{15}-O-				
11	*n*-C_8H_{17}-O-	27		42	
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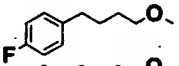
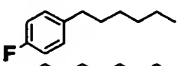
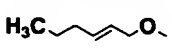
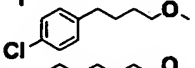
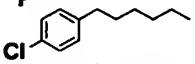
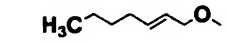
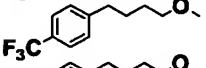
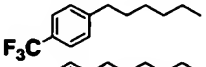
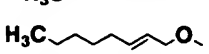
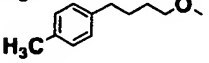
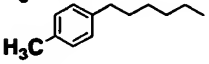
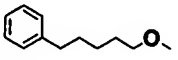
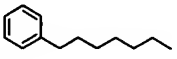
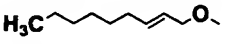
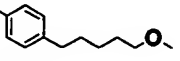
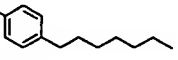
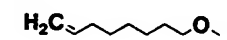
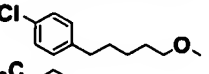
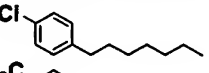
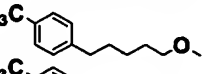
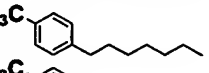
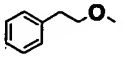
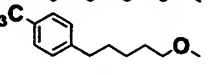
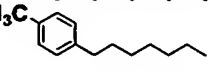
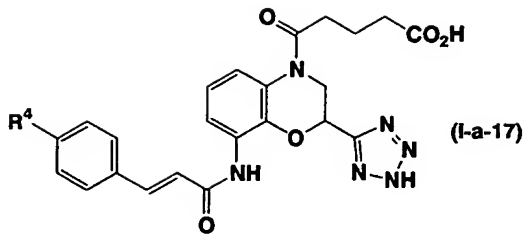
13		28		43	
14		29		44	
15		30		45	
16		31		46	
17		32		47	
18		33		48	
19		34		49	
20		35		50	
21		36		51	

Table 17



(I-a-17)

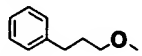
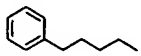
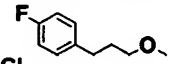
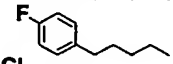
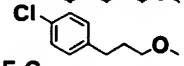
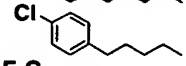
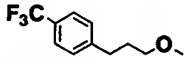
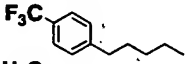
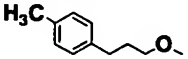
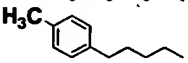
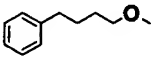
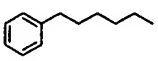
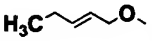
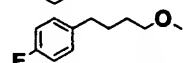
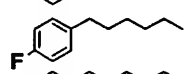
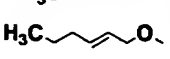
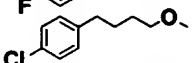
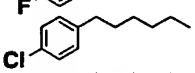
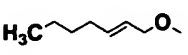
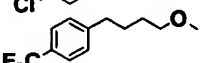
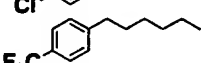
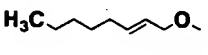
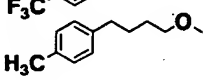
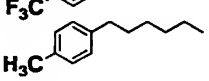
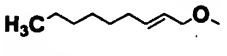
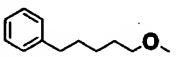
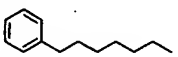
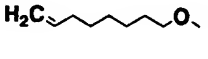
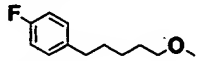
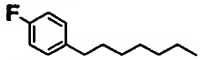
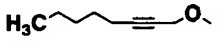
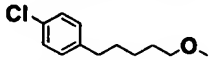
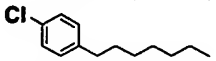
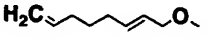
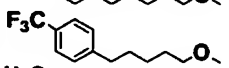
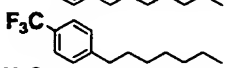
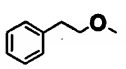
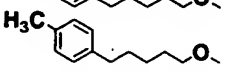
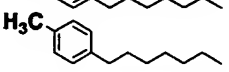
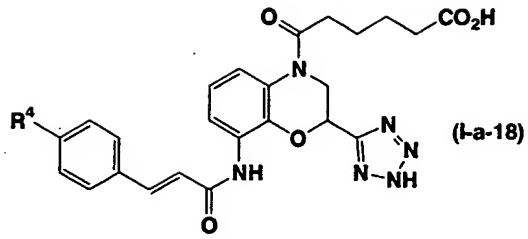
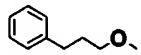
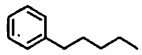
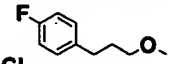
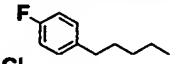
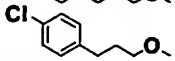
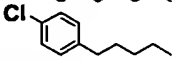
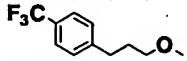
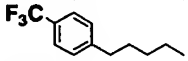
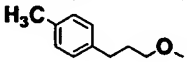
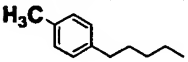
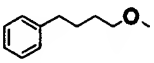
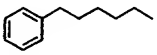
	R4		R4		R4
1	*n*-C_4H_9-	22		37	
2	*n*-C_5H_{11}-				
3	*n*-C_6H_{13}-	23		38	
4	*n*-C_7H_{15}-				
5	*n*-C_8H_{17}-	24		39	
6	*n*-C_9H_{19}-				
7	*n*-C_4H_9-O-	25		40	
8	*n*-C_5H_{11}-O-				
9	*n*-C_6H_{13}-O-	26		41	
10	*n*-C_7H_{15}-O-				
11	*n*-C_8H_{17}-O-	27		42	
12	*n*-C_9H_{19}-O-				
13		28		43	
14		29		44	
15		30		45	
16		31		46	
17		32		47	
18		33		48	
19		34		49	
20		35		50	
21		36		51	

Table 18



(I-a-18)

	R^4		R^4		R^4
1	*n*-C_4H_9-	22		37	
2	*n*-C_5H_{11}-	23		38	
3	*n*-C_6H_{13}-	24		39	
4	*n*-C_7H_{15}-	25		40	
5	*n*-C_8H_{17}-	26		41	
6	*n*-C_9H_{19}-				
7	*n*-C_4H_9-O-	27		42	
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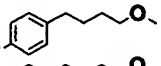
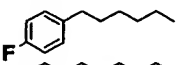
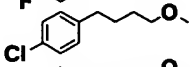
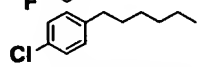
9	*n*-C_6H_{13}-O-	28		43	
10	*n*-C_7H_{15}-O-				
11	*n*-C_8H_{17}-O-	29		44	
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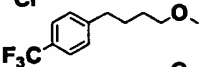
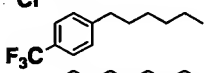
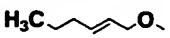
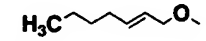
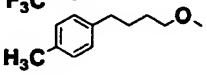
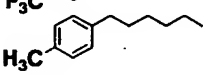
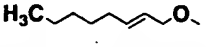
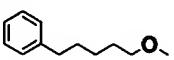
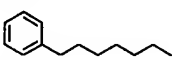
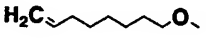
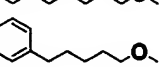
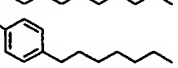
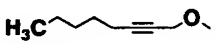
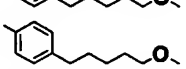
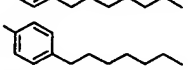
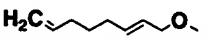
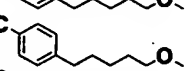
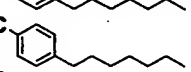
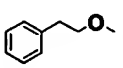
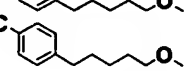
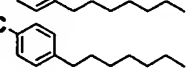
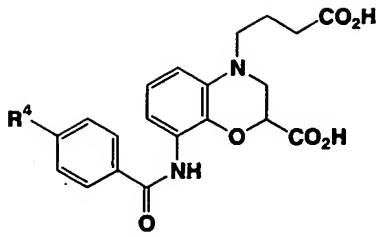
13		30		45	
14					
15		31		46	
16					
17		32		47	
18		33		48	
19		34		49	
20		35		50	
21		36		51	

Table 19



(I-a-19)

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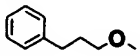
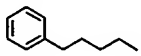
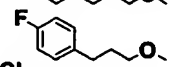
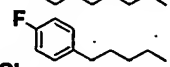
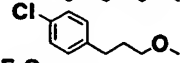
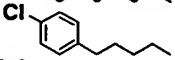
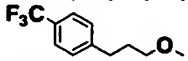
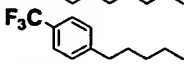
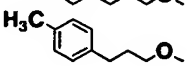
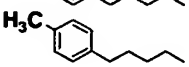
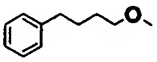
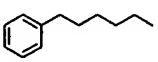
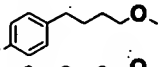
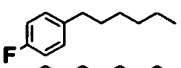
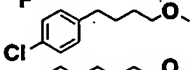
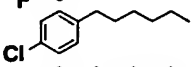
1	*n*-C_4H_9-	22		37	
2	*n*-C_5H_{11}-	23		38	
3	*n*-C_6H_{13}-	24		39	
4	*n*-C_7H_{15}-	25		40	
5	*n*-C_8H_{17}-	26		41	
6	*n*-C_9H_{19}-				
7	*n*-C_4H_9-O-	27		42	
8	*n*-C_5H_{11}-O-				
9	*n*-C_6H_{13}-O-	28		43	
10	*n*-C_7H_{15}-O-				
11	*n*-C_8H_{17}-O-	29		44	
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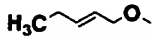
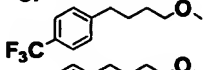
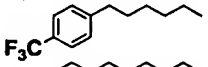
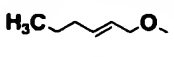
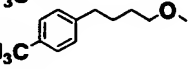
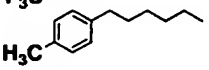
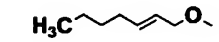
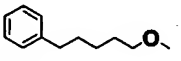
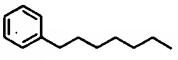
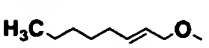
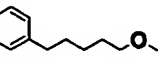
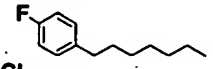
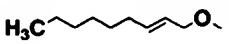
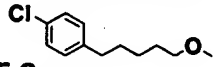
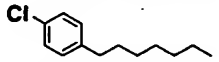
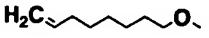
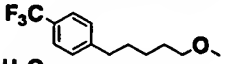
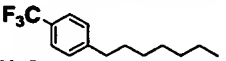
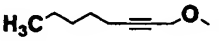
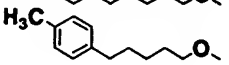
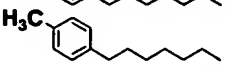
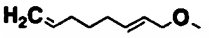
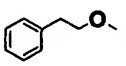
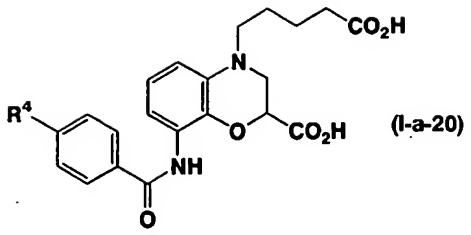
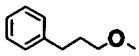
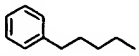
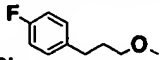
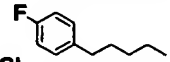
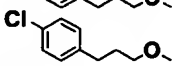
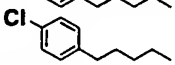
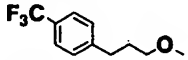
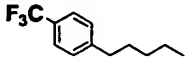
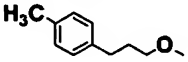
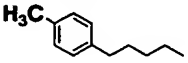
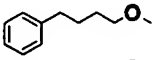
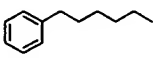
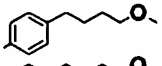
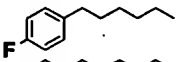
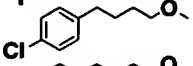
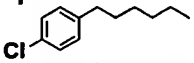
13		30		45	
14		31		46	
15		32		47	
16		33		48	
17		34		49	
18		35		50	
19		36		51	
20					
21					

Table 20



(I-a-20)

	R4		R4		R4
1	*n*-C_4H_9-	22		37	
2	*n*-C_5H_{11}-	23		38	
3	*n*-C_6H_{13}-	24		39	
4	*n*-C_7H_{15}-	25		40	
5	*n*-C_8H_{17}-	26		41	
6	*n*-C_9H_{19}-				
7	*n*-C_4H_9-O-	27		42	
8	*n*-C_5H_{11}-O-				
9	*n*-C_6H_{13}-O-	28		43	
10	*n*-C_7H_{15}-O-				
11	*n*-C_8H_{17}-O-	29		44	
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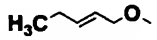
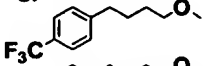
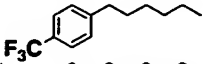
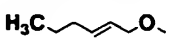
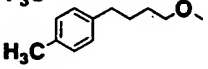
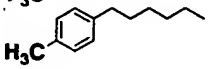
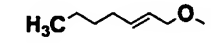
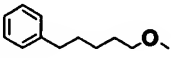
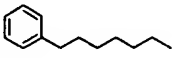
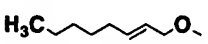
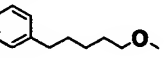
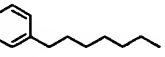
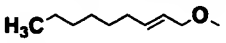
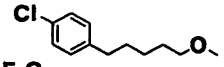
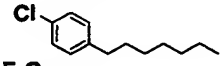
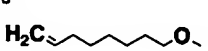
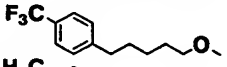
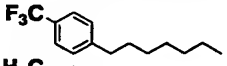
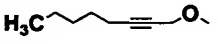
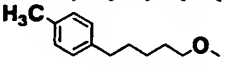
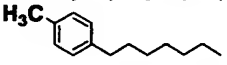
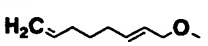
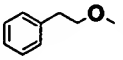
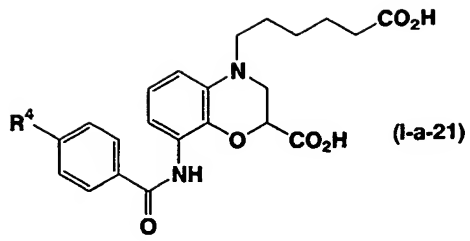
13		30		45	
14		31		46	
15		32		47	
16		33		48	
17		34		49	
18		35		50	
19		36		51	
20					
21					

Table 21



(I-a-21)

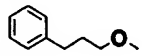
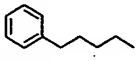
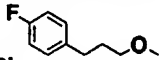
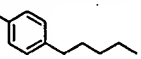
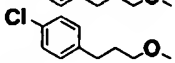
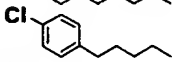
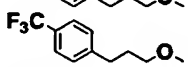
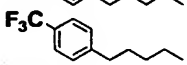
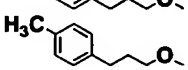
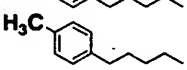
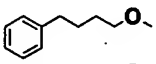
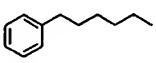
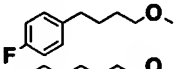
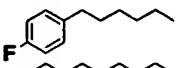
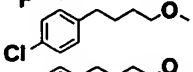
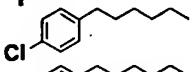
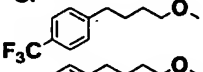
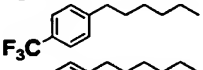
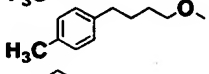
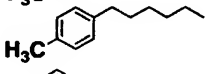
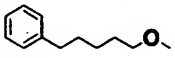
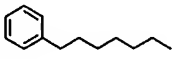
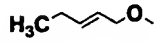
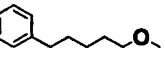
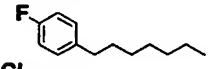
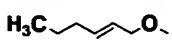
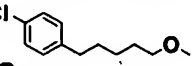
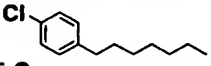
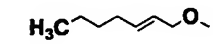
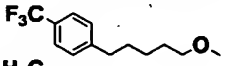
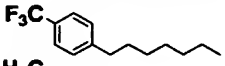
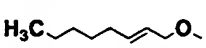
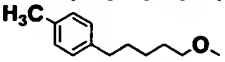
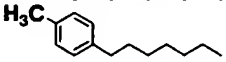
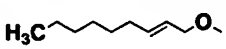
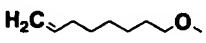
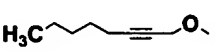
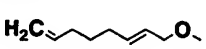
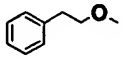
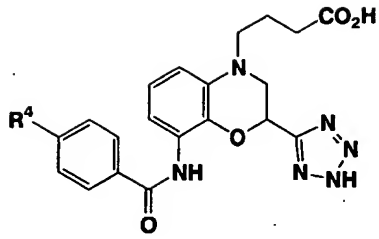
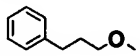
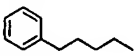
	R^4		R^4		R^4
1	*n*-C_4H_9-	22		37	
2	*n*-C_5H_{11}-	23		38	
3	*n*-C_6H_{13}-	24		39	
4	*n*-C_7H_{15}-	25		40	
5	*n*-C_8H_{17}-	26		41	
6	*n*-C_9H_{19}-				
7	*n*-C_4H_9-O-	27		42	
8	*n*-C_5H_{11}-O-	28		43	
9	*n*-C_6H_{13}-O-	29		44	
10	*n*-C_7H_{15}-O-	30		45	
11	*n*-C_8H_{17}-O-	31		46	
12	*n*-C_9H_{19}-O-	32		47	
13		33		48	
14		34		49	
15		35		50	
16		36		51	
17					
18					
19					
20					
21					

Table 22



(I-a-22)

	R^4		R^4		R^4
1	*n*-C_4H_9-	22		37	
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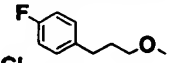
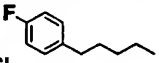
3	*n*-C_6H_{13}-	23		38	
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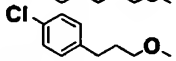
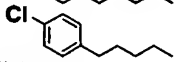
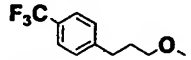
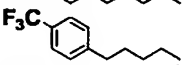
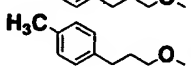
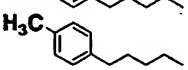
5	*n*-C_8H_{17}-	24		39	
6	*n*-C_9H_{19}-				
7	*n*-C_4H_9-O-	25		40	
8	*n*-C_5H_{11}-O-				
9	*n*-C_6H_{13}-O-	26		41	
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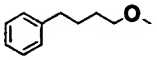
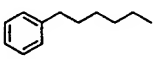
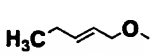
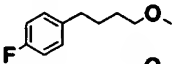
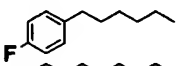
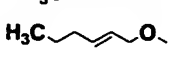
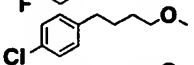
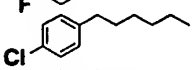
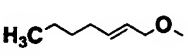
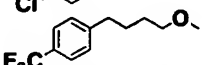
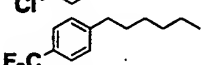
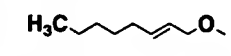
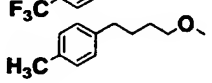
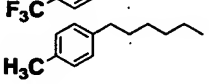
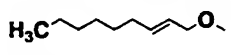
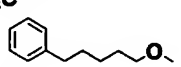
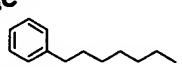
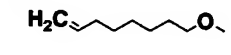
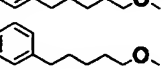
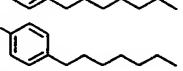
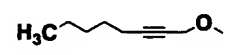
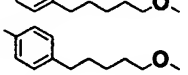
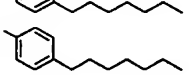
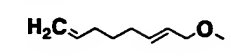
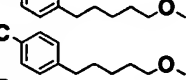
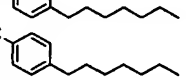
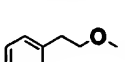
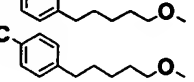
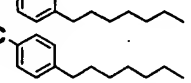
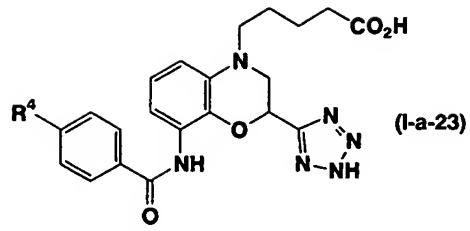
11	*n*-C_8H_{17}-O-	27		42	
12	*n*-C_9H_{19}-O-				
13		28		43	
14		29		44	
15		30		45	
16		31		46	
17		32		47	
18		33		48	
19		34		49	
20		35		50	
21		36		51	

Table 23



(I-a-23)

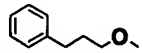
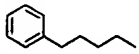
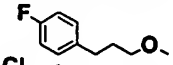
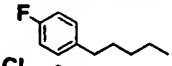
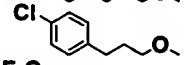
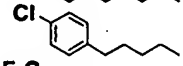
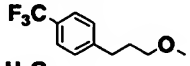
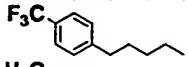
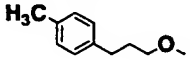
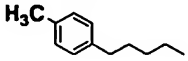
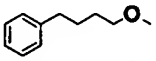
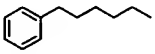
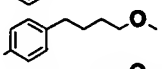
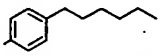
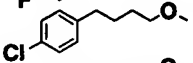
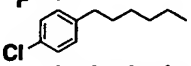
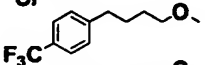
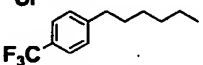
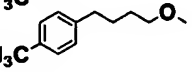
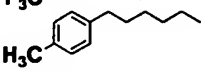
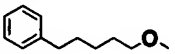
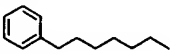
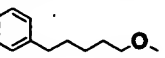
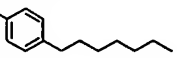
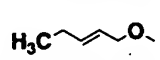
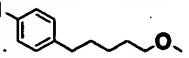
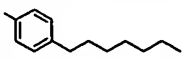
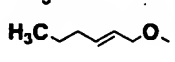
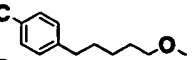
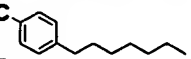
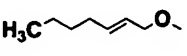
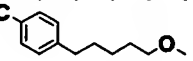
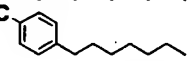
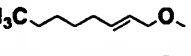
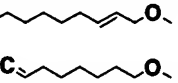
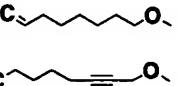
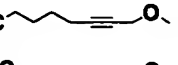
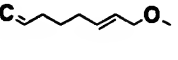
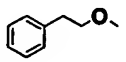
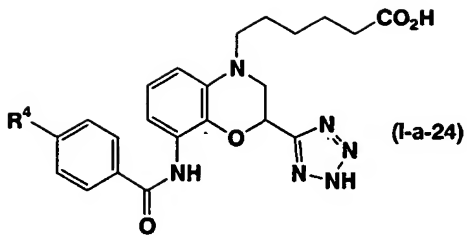
	R4		R4		R4
1	*n*-C_4H_9-	22		37	
2	*n*-C_5H_{11}-	23		38	
3	*n*-C_6H_{13}-	24		39	
4	*n*-C_7H_{15}-	25		40	
5	*n*-C_8H_{17}-	26		41	
6	*n*-C_9H_{19}-	27		42	
7	*n*-C_4H_9-O-	28		43	
8	*n*-C_5H_{11}-O-	29		44	
9	*n*-C_6H_{13}-O-	30		45	
10	*n*-C_7H_{15}-O-	31		46	
11	*n*-C_8H_{17}-O-	32		47	
12	*n*-C_9H_{19}-O-	33		48	
13		34		49	
14		35		50	
15		36		51	
16					
17					
18					
19					
20					
21					

Table 24



(I-a-24)

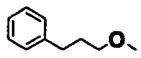
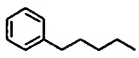
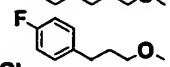
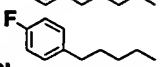
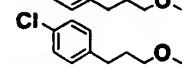
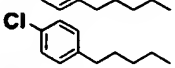
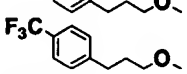
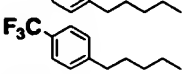
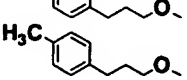
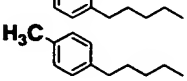
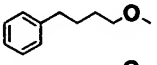
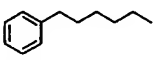
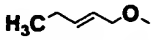
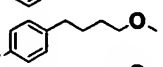
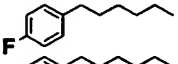
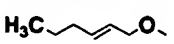
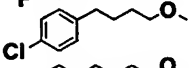
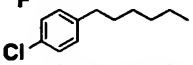
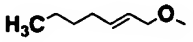
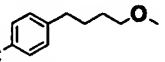
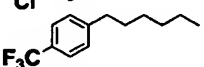
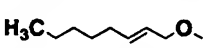
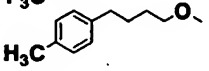
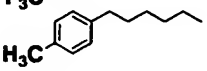
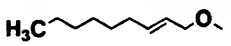
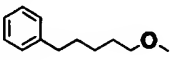
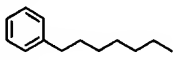
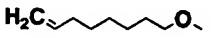
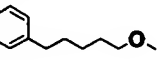
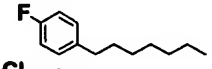
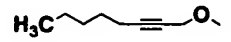
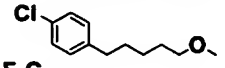
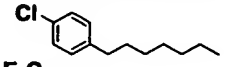
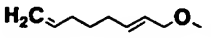
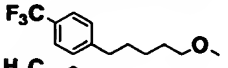
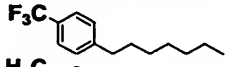
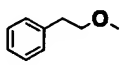
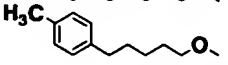
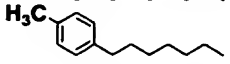
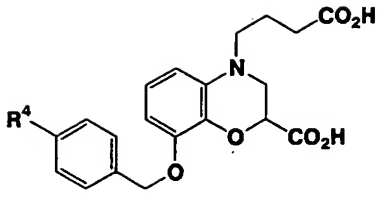
	R4		R4		R4
1	*n*-C_4H_9-	22		37	
2	*n*-C_5H_{11}-				
3	*n*-C_6H_{13}-	23		38	
4	*n*-C_7H_{15}-				
5	*n*-C_8H_{17}-	24		39	
6	*n*-C_9H_{19}-				
7	*n*-C_4H_9-O-	25		40	
8	*n*-C_5H_{11}-O-				
9	*n*-C_6H_{13}-O-	26		41	
10	*n*-C_7H_{15}-O-				
11	*n*-C_8H_{17}-O-	27		42	
12	*n*-C_9H_{19}-O-				
13		28		43	
14		29		44	
15		30		45	
16		31		46	
17		32		47	
18		33		48	
19		34		49	
20		35		50	
21		36		51	

Table 25



(I-a-25)

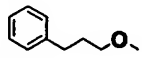
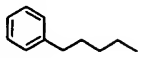
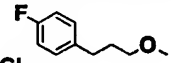
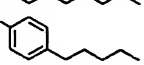
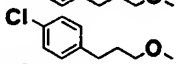
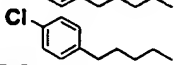
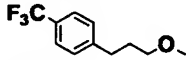
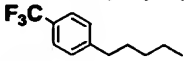
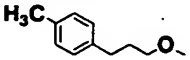
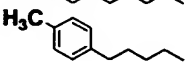
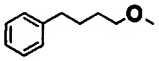
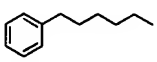
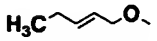
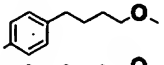
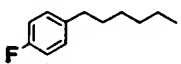
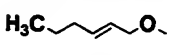
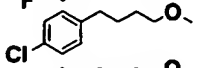
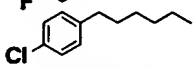
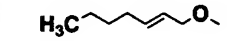
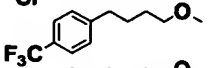
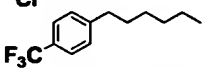
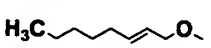
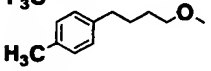
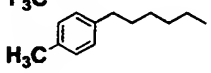
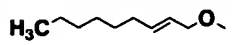
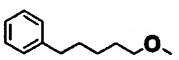
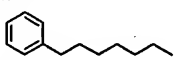
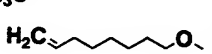
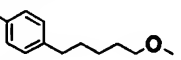
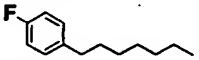
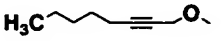
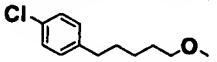
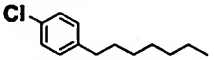
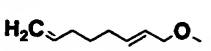
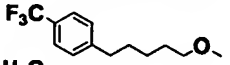
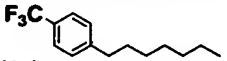
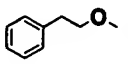
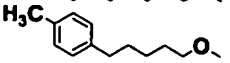
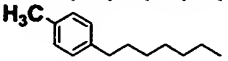
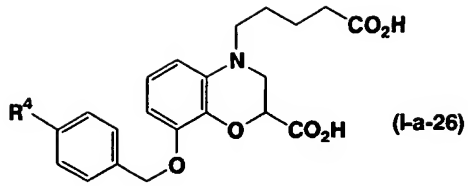
	R^4		R^4		R^4
1	*n*-C_4H_9-	22		37	
2	*n*-C_5H_{11}-				
3	*n*-C_6H_{13}-	23		38	
4	*n*-C_7H_{15}-				
5	*n*-C_8H_{17}-	24		39	
6	*n*-C_9H_{19}-				
7	*n*-C_4H_9-O-	25		40	
8	*n*-C_5H_{11}-O-				
9	*n*-C_6H_{13}-O-	26		41	
10	*n*-C_7H_{15}-O-				
11	*n*-C_8H_{17}-O-	27		42	
12	*n*-C_9H_{19}-O-				
13		28		43	
14		29		44	
15		30		45	
16		31		46	
17		32		47	
18		33		48	
19		34		49	
20		35		50	
21		36		51	

Table 26



(I-a-26)

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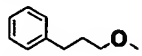
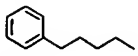
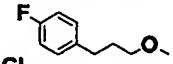
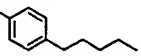
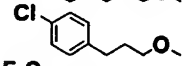
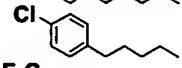
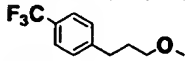
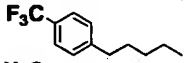
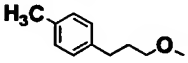
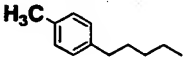
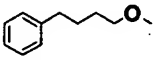
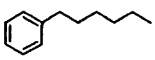
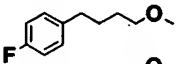
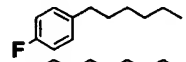
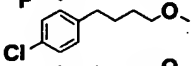
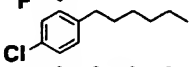
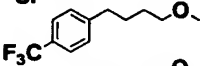
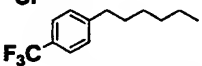
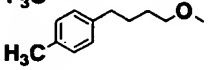
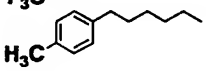
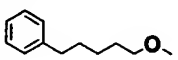
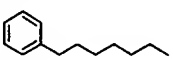
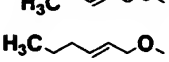
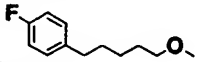
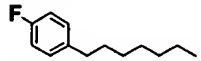
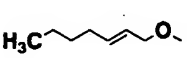
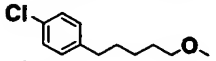
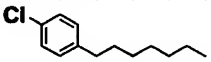
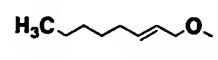
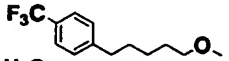
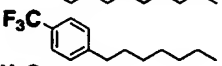
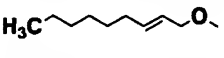
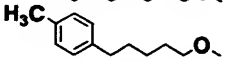
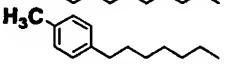
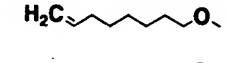
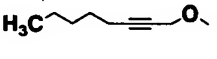
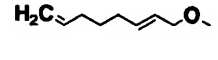
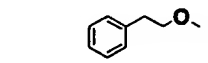
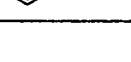
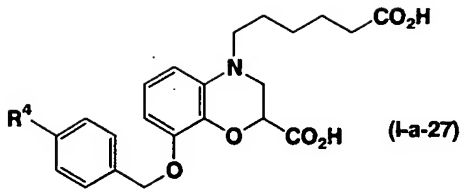
1	*n*-C_4H_9-	22		37	
2	*n*-C_5H_{11}-	23		38	
3	*n*-C_6H_{13}-	24		39	
4	*n*-C_7H_{15}-	25		40	
5	*n*-C_8H_{17}-	26		41	
6	*n*-C_9H_{19}-				
7	*n*-C_4H_9-O-	27		42	
8	*n*-C_5H_{11}-O-	28		43	
9	*n*-C_6H_{13}-O-	29		44	
10	*n*-C_7H_{15}-O-	30		45	
11	*n*-C_8H_{17}-O-	31		46	
12	*n*-C_9H_{19}-O-	32		47	
13		33		48	
14		34		49	
15		35		50	
16		36		51	
17					
18					
19					
20					
21					

Table 27



(I-a-27)

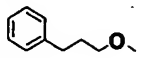
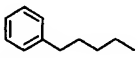
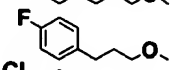
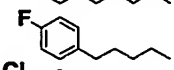
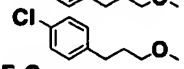
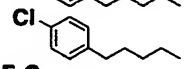
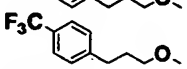
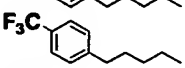
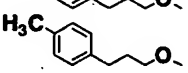
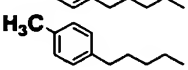
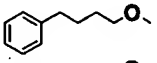
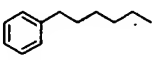
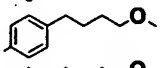
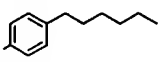
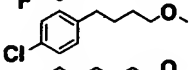
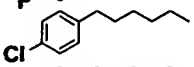
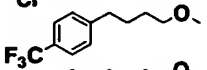
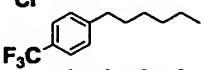
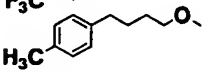
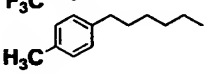
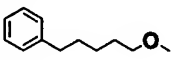
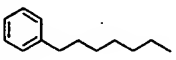
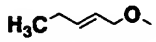
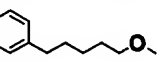
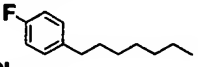
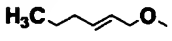
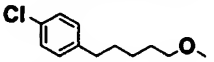
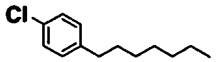
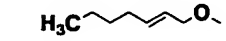
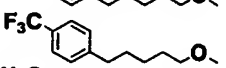
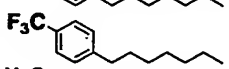
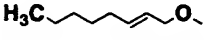
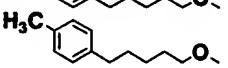
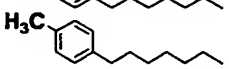
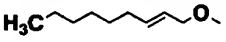
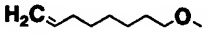
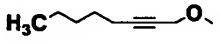
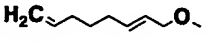
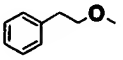
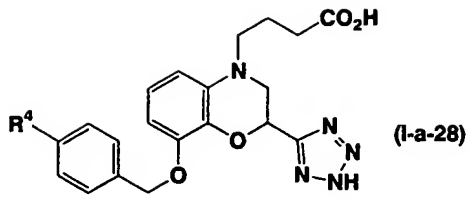
	R4		R4		R4
1	*n*-C_4H_9-	22		37	
2	*n*-C_5H_{11}-	23		38	
3	*n*-C_6H_{13}-	24		39	
4	*n*-C_7H_{15}-	25		40	
5	*n*-C_8H_{17}-	26		41	
6	*n*-C_9H_{19}-				
7	*n*-C_4H_9-O-	27		42	
8	*n*-C_5H_{11}-O-	28		43	
9	*n*-C_6H_{13}-O-	29		44	
10	*n*-C_7H_{15}-O-	30		45	
11	*n*-C_8H_{17}-O-	31		46	
12	*n*-C_9H_{19}-O-	32		47	
13		33		48	
14		34		49	
15		35		50	
16		36		51	
17					
18					
19					
20					
21					

Table 28



(I-a-28)

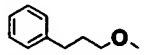
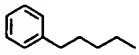
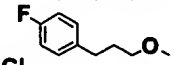
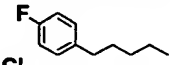
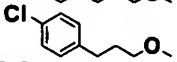
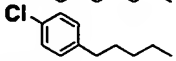
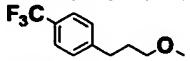
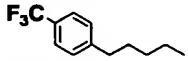
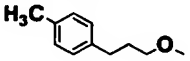
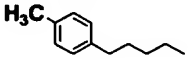
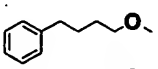
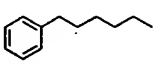
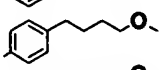
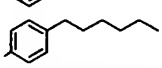
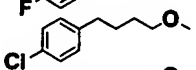
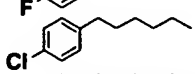
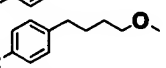
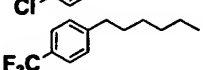
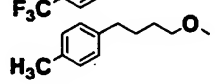
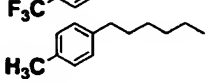
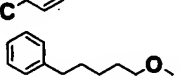
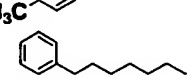
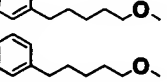
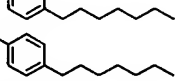
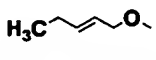
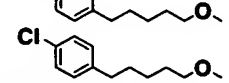
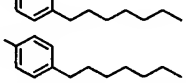
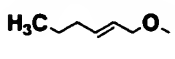
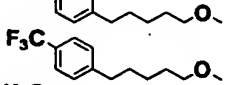
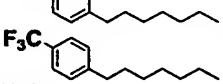
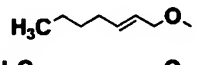
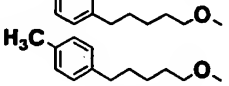
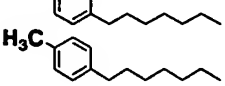
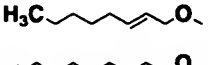
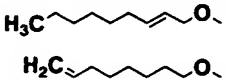
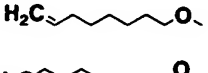
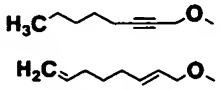
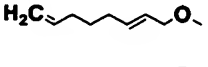
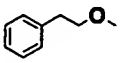
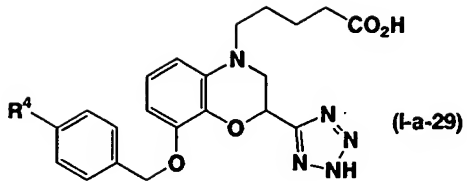
	R4		R4		R4
1	*n*-C_4H_9-	22		37	
2	*n*-C_5H_{11}-	23		38	
3	*n*-C_6H_{13}-	24		39	
4	*n*-C_7H_{15}-	25		40	
5	*n*-C_8H_{17}-	26		41	
6	*n*-C_9H_{19}-	27		42	
7	*n*-C_4H_9-O-	28		43	
8	*n*-C_5H_{11}-O-	29		44	
9	*n*-C_6H_{13}-O-	30		45	
10	*n*-C_7H_{15}-O-	31		46	
11	*n*-C_8H_{17}-O-	32		47	
12	*n*-C_9H_{19}-O-	33		48	
13		34		49	
14		35		50	
15		36		51	
16					
17					
18					
19					
20					
21					

Table 29



(I-a-29)

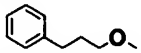
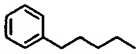
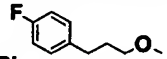
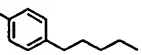
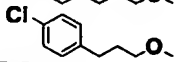
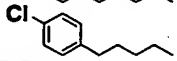
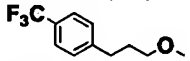
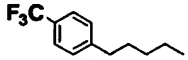
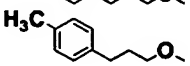
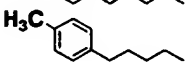
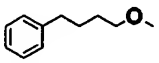
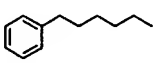
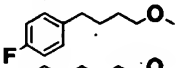
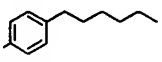
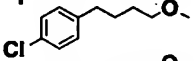
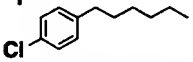
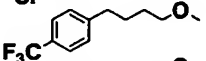
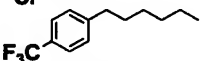
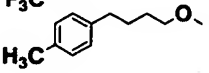
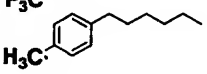
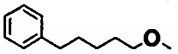
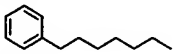
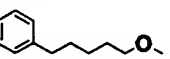
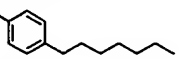
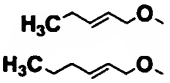
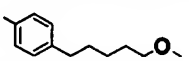
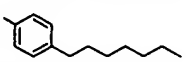
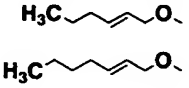
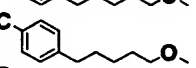
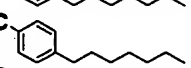
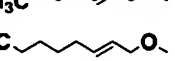
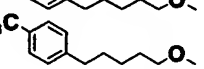
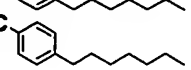
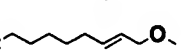
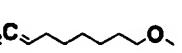
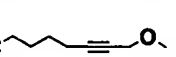
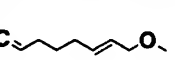
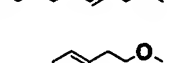
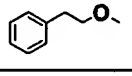
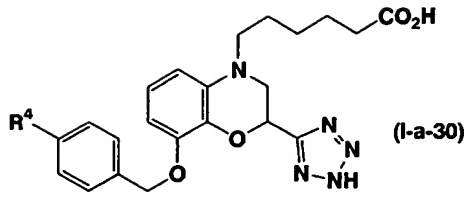
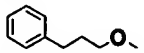
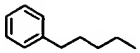
	R^4		R^4		R^4
1	*n*-C_4H_9-	22		37	
2	*n*-C_5H_{11}-	23		38	
3	*n*-C_6H_{13}-	24		39	
4	*n*-C_7H_{15}-	25		40	
5	*n*-C_8H_{17}-	26		41	
6	*n*-C_9H_{19}-	27		42	
7	*n*-C_4H_9-O-	28		43	
8	*n*-C_5H_{11}-O-	29		44	
9	*n*-C_6H_{13}-O-	30		45	
10	*n*-C_7H_{15}-O-	31		46	
11	*n*-C_8H_{17}-O-	32		47	
12	*n*-C_9H_{19}-O-	33		48	
13		34		49	
14		35		50	
15		36		51	
16					
17					
18					
19					
20					
21					

Table 30



(I-a-30)

	R4		R4		R4
1	*n*-C_4H_9-	22		37	
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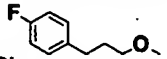
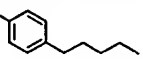
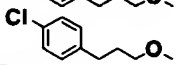
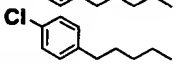
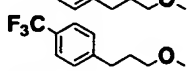
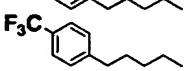
3	*n*-C_6H_{13}-	23		38	
4	*n*-C_7H_{15}-				
5	*n*-C_8H_{17}-	24		39	
6	*n*-C_9H_{19}-				
7	*n*-C_4H_9-O-	25		40	
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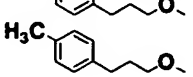
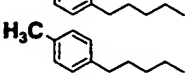
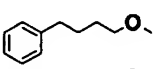
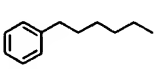
9	*n*-C_6H_{13}-O-	26		41	
10	*n*-C_7H_{15}-O-				
11	*n*-C_8H_{17}-O-	27		42	
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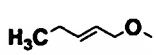
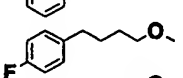
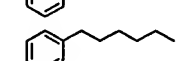
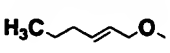
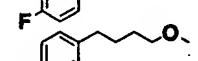
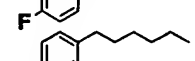
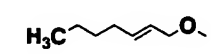
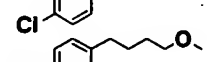
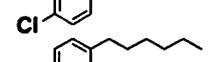
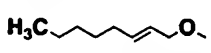
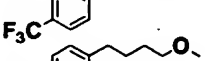
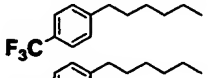
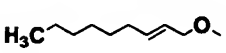
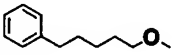
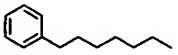
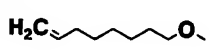
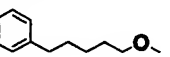
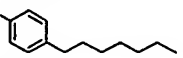
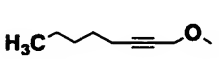
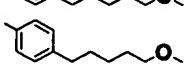
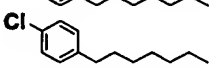
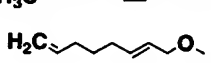
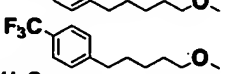
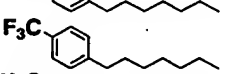
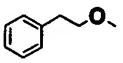
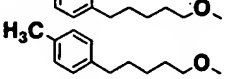
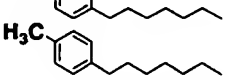
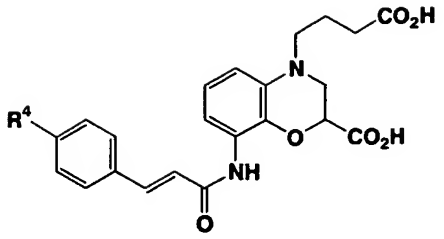
13		28		43	
14		29		44	
15		30		45	
16		31		46	
17		32		47	
18		33		48	
19		34		49	
20		35		50	
21		36		51	

Table 31



(I-a-31)

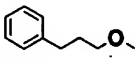
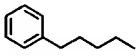
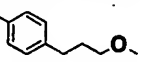
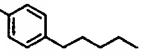
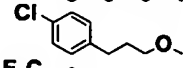
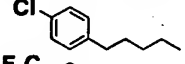
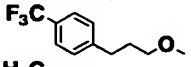
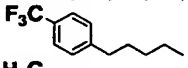
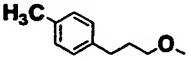
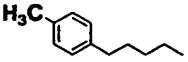
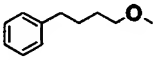
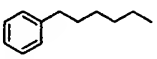
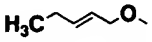
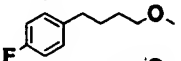
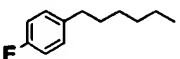
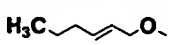
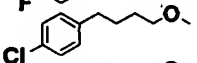
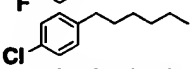
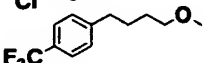
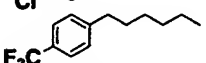
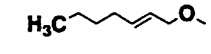
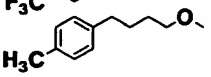
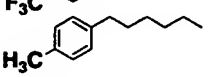
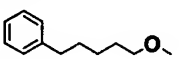
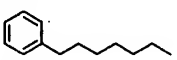
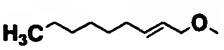
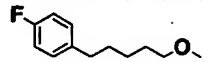
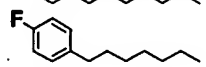
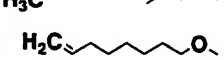
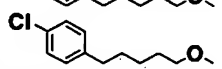
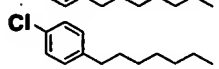
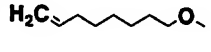
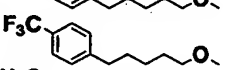
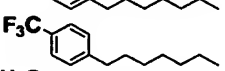
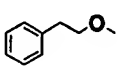
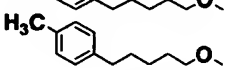
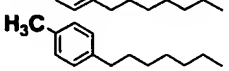
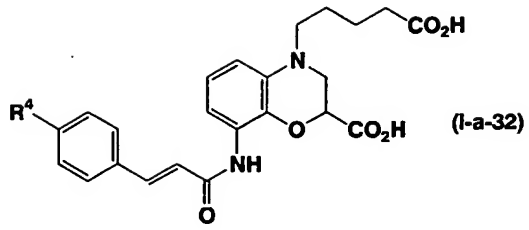
	R^4		R^4		R^4
1	*n*-C_4H_9-	22		37	
2	*n*-C_5H_{11}-				
3	*n*-C_6H_{13}-	23		38	
4	*n*-C_7H_{15}-				
5	*n*-C_8H_{17}-	24		39	
6	*n*-C_9H_{19}-				
7	*n*-C_4H_9-O-	25		40	
8	*n*-C_5H_{11}-O-				
9	*n*-C_6H_{13}-O-	26		41	
10	*n*-C_7H_{15}-O-				
11	*n*-C_8H_{17}-O-	27		42	
12	*n*-C_9H_{19}-O-				
13		28		43	
14		29		44	
15		30		45	
16		31		46	
17		32		47	
18		33		48	
19		34		49	
20		35		50	
21		36		51	

Table 32



(I-a-32)

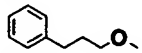
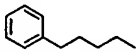
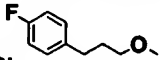
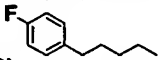
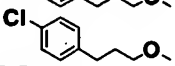
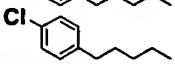
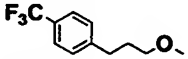
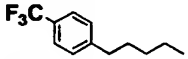
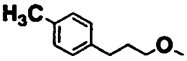
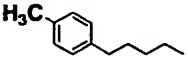
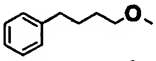
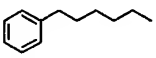
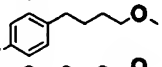
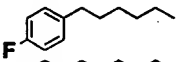
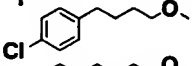
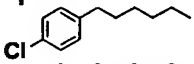
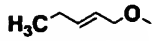
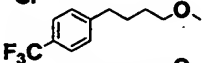
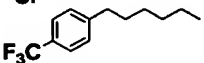
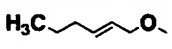
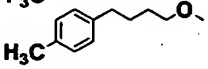
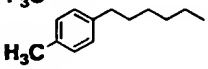
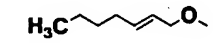
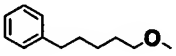
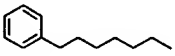
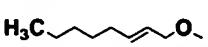
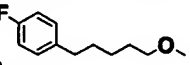
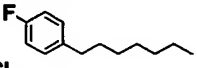
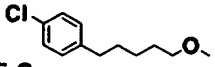
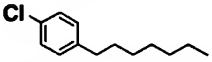
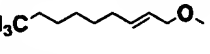
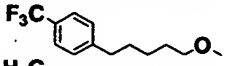
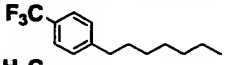
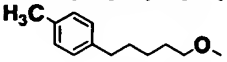
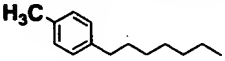
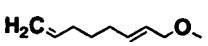
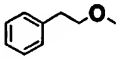
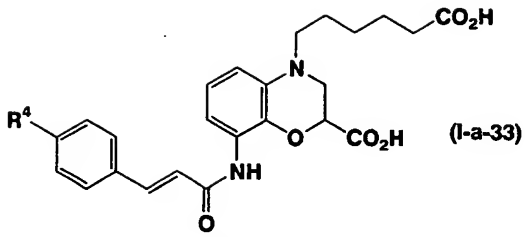
	R^4		R^4		R^4
1	*n*-C_4H_9-	22		37	
2	*n*-C_5H_{11}-	23		38	
3	*n*-C_6H_{13}-	24		39	
4	*n*-C_7H_{15}-	25		40	
5	*n*-C_8H_{17}-	26		41	
6	*n*-C_9H_{19}-				
7	*n*-C_4H_9-O-	27		42	
8	*n*-C_5H_{11}-O-				
9	*n*-C_6H_{13}-O-	28		43	
10	*n*-C_7H_{15}-O-				
11	*n*-C_8H_{17}-O-	29		44	
12	*n*-C_9H_{19}-O-				
13		30		45	
14		31		46	
15		32		47	
16		33		48	
17		34		49	
18		35		50	
19		36		51	
20					
21					

Table 33



(I-a-33)

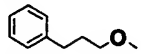
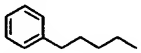
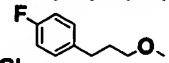
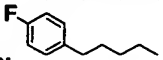
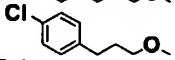
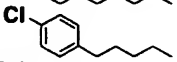
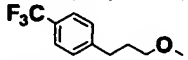
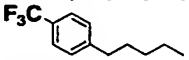
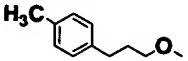
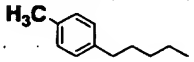
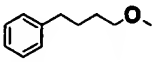
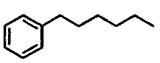
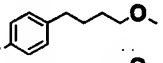
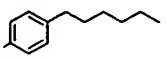
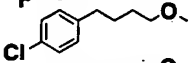
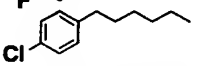
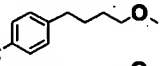
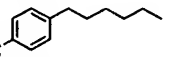
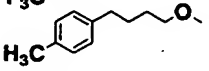
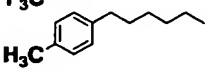
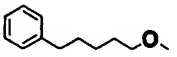
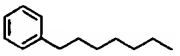
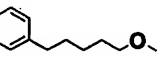
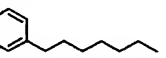
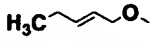
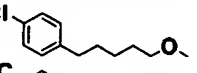
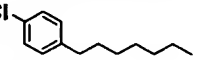
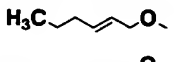
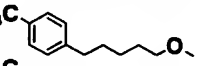
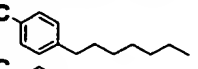
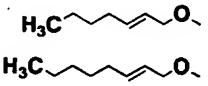
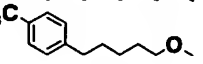
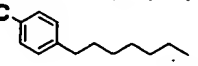
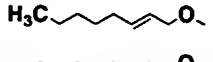
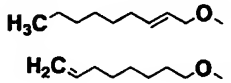
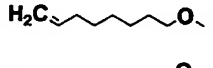
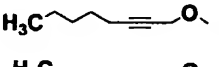
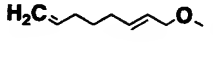
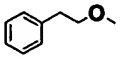
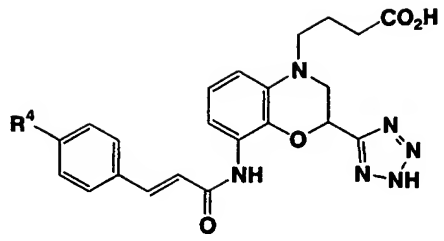
	R^4		R^4		R^4
1	*n*-C_4H_9-	22		37	
2	*n*-C_5H_{11}-	23		38	
3	*n*-C_6H_{13}-	24		39	
4	*n*-C_7H_{15}-	25		40	
5	*n*-C_8H_{17}-	26		41	
6	*n*-C_9H_{19}-	27		42	
7	*n*-C_4H_9-O-	28		43	
8	*n*-C_5H_{11}-O-	29		44	
9	*n*-C_6H_{13}-O-	30		45	
10	*n*-C_7H_{15}-O-	31		46	
11	*n*-C_8H_{17}-O-	32		47	
12	*n*-C_9H_{19}-O-	33		48	
13		34		49	
14		35		50	
15		36		51	
16					
17					
18					
19					
20					
21					

Table 34



(I-a-34)

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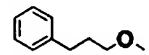
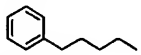
1	*n*-C_4H_9-	22		37	
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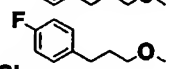
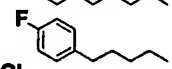
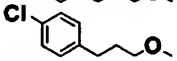
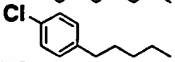
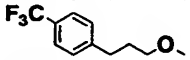
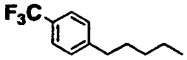
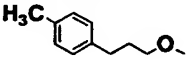
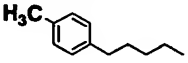
3	*n*-C_6H_{13}-	23		38	
4	*n*-C_7H_{15}-				
5	*n*-C_8H_{17}-	24		39	
6	*n*-C_9H_{19}-				
7	*n*-C_4H_9-O-	25		40	
8	*n*-C_5H_{11}-O-				
9	*n*-C_6H_{13}-O-	26		41	
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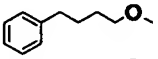
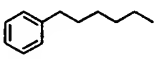
11	*n*-C_8H_{17}-O-	27		42	
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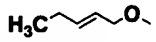
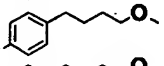
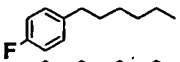
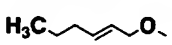
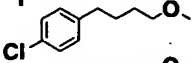
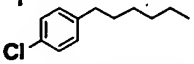
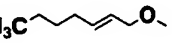
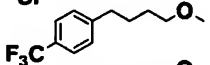
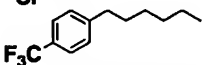
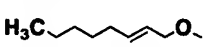
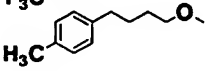
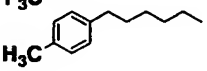
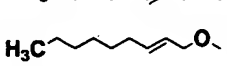
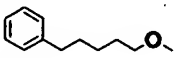
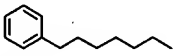
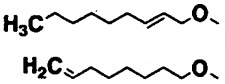
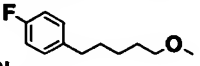
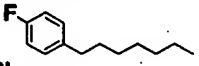
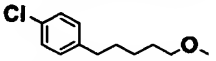
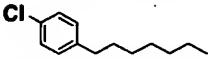
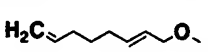
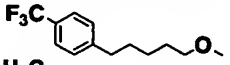
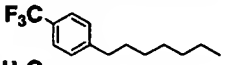
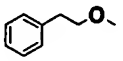
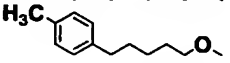
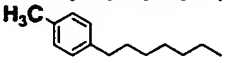
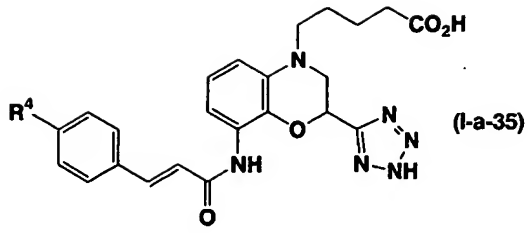
13		28		43	
14		29		44	
15		30		45	
16		31		46	
17		32		47	
18		33		48	
19		34		49	
20		35		50	
21		36		51	

Table 35



(I-a-35)

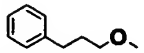
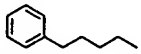
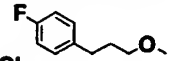
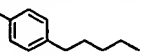
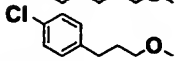
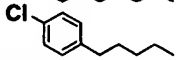
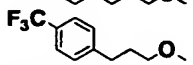
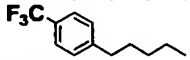
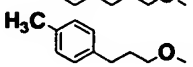
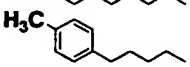
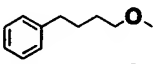
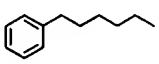
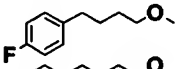
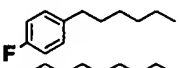
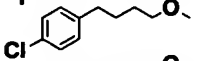
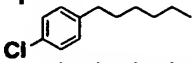
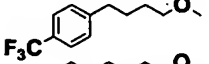
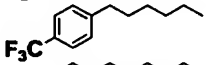
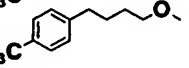
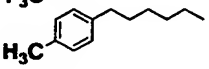
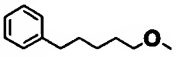
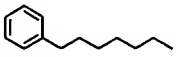
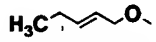
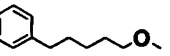
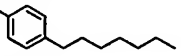
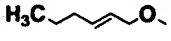
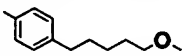
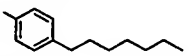
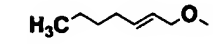
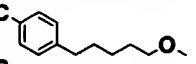
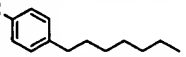
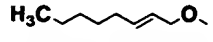
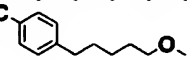
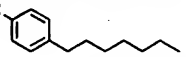
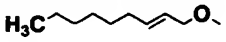
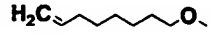
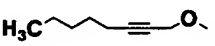
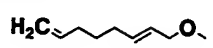
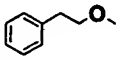
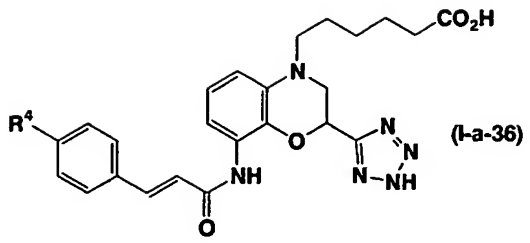
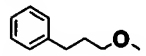
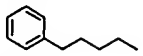
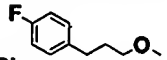
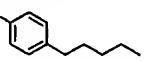
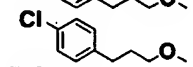
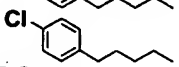
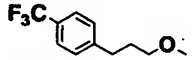
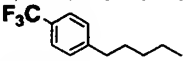
	R^4		R^4		R^4
1	*n*-C_4H_9-	22		37	
2	*n*-C_5H_{11}-	23		38	
3	*n*-C_6H_{13}-	24		39	
4	*n*-C_7H_{15}-	25		40	
5	*n*-C_8H_{17}-	26		41	
6	*n*-C_9H_{19}-				
7	*n*-C_4H_9-O-	27		42	
8	*n*-C_5H_{11}-O-	28		43	
9	*n*-C_6H_{13}-O-	29		44	
10	*n*-C_7H_{15}-O-	30		45	
11	*n*-C_8H_{17}-O-	31		46	
12	*n*-C_9H_{19}-O-	32		47	
13		33		48	
14		34		49	
15		35		50	
16		36		51	
17					
18					
19					
20					
21					

Table 36



(I-a-36)

	R4		R4		R4
1	*n*-C_4H_9-	22		37	
2	*n*-C_5H_{11}-				
3	*n*-C_6H_{13}-	23		38	
4	*n*-C_7H_{15}-				
5	*n*-C_8H_{17}-	24		39	
6	*n*-C_9H_{19}-				
7	*n*-C_4H_9-O-	25		40	
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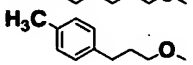
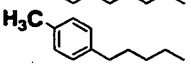
9	*n*-C_6H_{13}-O-	26		41	
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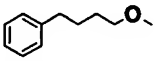
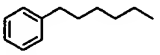
11	*n*-C_8H_{17}-O-	27		42	
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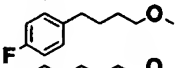
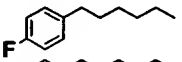
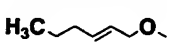
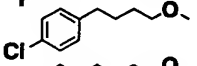
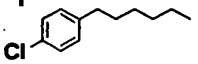
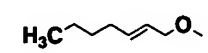
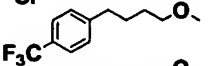
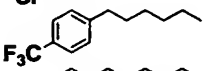
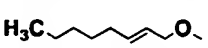
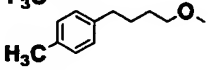
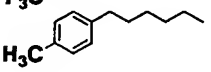
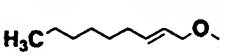
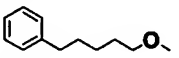
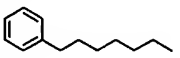
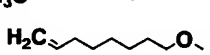
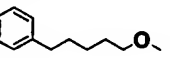
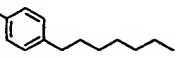
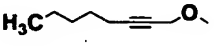
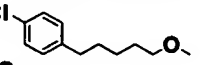
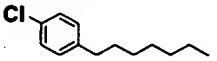
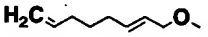
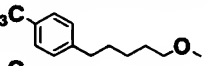
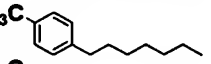
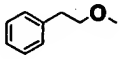
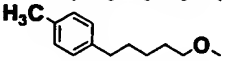
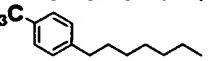
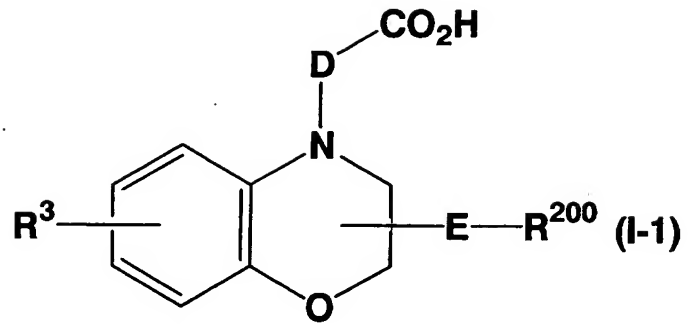
13		28		43	
14		29		44	
15		30		45	
16		31		46	
17		32		47	
18		33		48	
19		34		49	
20		35		50	
21		36		51	

The compound of formula (I) of the present invention may be prepared by known methods, for example, the following methods, the pursuant methods thereof or the methods described in Examples. In each following method for the preparation, salts of the starting materials may be used. The above pharmaceutical acceptable salts of the compound (I) may be used.

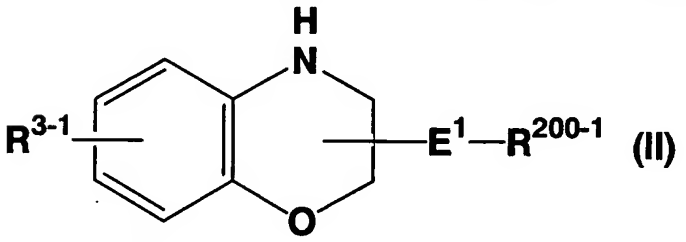
a) Among the compound of formula (I), the compound wherein ring A is benzene, ring B is morphorine, R^1 is carboxy, R^2 is carboxy or 5-tetrazolyl, i.e., the compound of formula (I-1)



(I-1)

(wherein R^{200} is carboxy or 5-tetrazolyl, and the other symbols have the same meanings as hereinbefore) may be prepared according to the following method.

The compound of formula (I-1) may be prepared by subjecting the compound of formula (II)



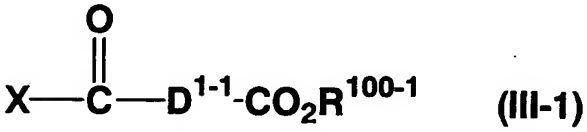
(II)

(wherein R^{200-1} is carboxy or 5-tetrazolyl protected by a protective group, R^{3-1} and E^1 have the same meaning as R^3 and E, in which the carboxy, hydroxy, amino or thiol included in the groups represented by R^{3-1} and E^1 are protected if necessary) to a reaction with the compound of formula (III)

(III)

(wherein X is a leaving group such as, for example, halogen, mesyloxy, tosyloxy, oxo, etc., and R^{100-1} is a protective group of carboxy, D^1 has the same meaning as D, and carboxy, hydroxy, amino or thiol included in the groups represented by R^{3-1} and E^1 are protected if necessary.), optionally followed by subjecting to a deprotection reaction of the protective groups.

The reaction of the compound wherein X-D^1 is an active acyl group among the compounds of formula (III), i.e. the compound of formula (III-1)



(III-1)

(wherein D^{1-1} represents a spacer consisting of 1-7 of atom in the main chain, in which the carboxy, hydroxy, amino or thiol in the groups represented by R^{3-1} and E^1 are protected if necessary, and the other symbols have the same meanings as hereinbefore) and the compound of formula (II), may be carried out by, for example,

(1) a method using acid halide,

(2) a method using mixed anhydride,

(3) a method using a condensing agent, etc.

To explain these methods specifically;

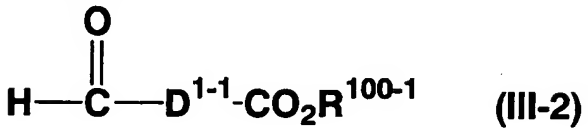
(1) the method using acid halide is carried out, for example, by subjecting a carboxylic acid to a reaction with an acid-halogenating agent (e.g. oxalyl chloride, thionyl chloride, etc.) in an organic solvent (e.g. chloroform, dichloromethane, diethyl ether, tetrahydrofuran, dimethoxyethane etc.) or without a solvent, at a temperature of about -20°C to a refluxing temperature, and then subjecting the thus obtained acid halide to a reaction with an amine in the presence of a base (e.g. pyridine, triethylamine, dimethylaniline, dimethylaminopyridine, diisopropylethylamine, etc.) in an organic solvent (e.g. chloroform, dichloromethane, diethyl ether, tetrahydrofuran, acetonitorile, acetic ether, etc.) at a temperature of about 0 to 40°C. Also, the reaction may be carried out by subjecting the thus obtained acidic halide to a reaction with an amine in an organic solvent (e.g. dioxane, tetrahydrofuran, dichloromethane, etc.) using an alkali aqueous solution (e.g. an aqueous solution of sodium bicarbonate, sodium hydroxide, etc.) in the presence or absence of a phase-transfer catalyst (e.g. tetraammonium salts such as tetrabutylammoniumchloride, triethylbenzylammoniumchloride, tri-n-octylmethylammoniumchloride, trimethyldecylammoniumchloride, tetramethylammoniumbromide, etc.) at a temperature between about 0 to 40°C;

(2) the method using mixed anhydride is carried out, for example, by subjecting a carboxylic acid to a reaction with an acid halide (e.g. pivaloyl chloride, tosyl chloride, mesylchloride, etc.) or an acid derivative (e.g.chloroethyl formate, chloroisobutyl formate, etc.) in an organic solvent (e.g. chloroform, dichloromethane, diethyl ether, tetrahydrofuran, etc.) or without a solvent in the presence of a base (pyridine, triethylamine, dimethylaniline, dimethylaminopyridine, diisopropylethylamine, etc.) at a temperature of 0 to 40°C, and then subjecting the thus obtained mixed anhydride to a reaction with an amine in an organic solvent (e.g. chloroform, methylene chloride, diethyl ether, tetrahydrofuran, etc.) at a temperature of about 0 to 40°C;

(3) the method using a condensing agent is carried out, for example, by subjecting a carboxylic acid to a reaction with an amine in an organic solvent (e.g. chloroform, methylene chloride, dimethylformamide, diethyl ether, tetrahydrofuran, etc.) or without a solvent, in the presence or absence of a base (e.g. pyridine, triethylamine, dimethylaniline, dimethylaminopyridine, etc.), using a condensing agent (e.g. 1,3-dicyclohexylcarbodiimide (DCC), 1-ethyl-3-[3-(dimethyl amino)propyl]carbodiimide (EDC), 1,1'-carbonyldiimidazole (CDI), 2-chloro-1-methylpyridinium iodide, 1-propylphosphonic acid cyclic anhydride (PPA), etc.) in the presence or absence of 1-hydroxybenzotriazole (1-HOBt) at a temperature of about 0 to 40°C.

The reactions (1), (2) and (3) are desirably carried out under atmosphere of inert gas (argon, nitrogen, etc.) and anhydrous conditions.

The reaction of the compound of formula (III), wherein X-D^1 possesses formyl group, i.e. the compound of formula (III-2)



(III-2)

(wherein all symbols have the same meaning as described hereinbefore) and the compound of formula (II) is carried out, for example, in an organic solvent (e.g. tetrahydrofuran, diethyl ether, dichloroethane, dichloromethane, dimethylformamide, acetic acid, methanol, ethanol or a mixture thereof, etc.), in the presence of a reducing agent (sodium triacetoxyborohydride, sodium cyanoborohydride, sodium borohydride, zinc borohydride, diisobutylaluminum hydride, etc.) at a temperature of about 0 to 40°C, or in a solvent (e.g. ethers such as tetrahydrofuran, dioxane, dimethoxyethane, diethyl ether, etc.; alcohols such as methanol, ethanol, etc.; benzenes such as benzene, toluene, etc.; ketones such as acetone, methylethyl ketone, etc.; nitriles such as acetonitrile etc.; amides such as dimethylformamide etc.; water, ethyl acetate, acetic acid, or a mixture of two or more thereof, etc.), in the presence of a catalyst (e.g. palladium carbon, palladium black, palladium hydroxide, platinum oxide, Raney nickel, etc.), under hydrogen atmosphere of normal or compressed pressure, at a temperature of about 0 to 200°C.

The deprotection reaction of the protective groups of carboxy, hydroxy, amino thiol or tetrazolyl is well-known and includes, for example,

(1) alkali hydrolysis,

(2) a deprotection under acidic conditions,

(3) a deprotection reaction by hydration,

(4) a deprotection of silyl group,

(5) a deprotection reaction using a metal,

(6) a deprotection reaction using a metal complex, etc.

To explain these methods concretely,

(1) the deprotection reaction by alkali hydrolysis is carried out, for example, in an organic solvent (methanol, tetrahydrofuran, 1,4-dioxane, etc.) using a hydroxide of alkali metals (sodium hydroxide, potassium hydroxide, lithium hydroxide, etc.), hydroxide of alkaline earth metals (barium hydroxide, calcium hydroxide, etc.), carbonate (sodium carbonate, potassium carbonate, etc.) or a solution thereof or a mixture thereof at a temperature of 0 to 40°C;

(2) the deprotection reaction under acidic conditions is carried out, for example, in an organic solvent (dichloromethane, chloroform, dioxane, ethyl acetate, anisole, etc.), in an organic acid (acetic acid, trifluoroacetic acid, methanesulfonic acid, p-toluenesulfonic acid, etc.) or an inorganic acid (hydrochloric acid, sulfuric acid, etc.) or a mixture thereof (hydrobromic acid/acetic acid, etc.) in the presence or absence of 2,2,2-trifluoroethanol at a temperature of 0

to 100°C;

(3) the deprotection reaction by hydration is, for example, carried out in a solvent (e.g. ethers such as tetrahydrofuran, 1,4-dioxane, dimethoxyethane, diethyl ether, etc.; alcohols such as methanol, ethanol, etc.; benzenes such as benzene, toluene, etc.; ketones such as acetone, methyl ethyl ketone, etc.; nitriles such as acetonitrile etc.; amides such as dimethylformamide etc.; water, ethyl acetate, acetic acid or a mixture of two or more thereof, etc.) in the presence of a catalyst (palladium-carbon, palladium black, palladium hydroxide, platinum oxide, Raney nickel, etc.) under the atmosphere of hydrogen of normal or suppressed pressure, or in the presence of ammonium formate at a temperature of 0 to 200°C;

(4) the deprotection of a silyl group is, for example, carried out in a water-miscible organic solvent (tetrahydrofuran, acetonitrile, etc.) using tetrabutylammonium fluoride at a temperature of 0 to 40°C;

(5) the deprotection reaction using a metal is carried out, for example, in an acidic solvent (acetic acid, a buffer of pH 4.2 to 7.2 or a mixture of the solution thereof and an organic solvent such as tetrahydrofuran etc.) in the presence of zinc powder at a temperature of 0 to 40°C optionally under sonication;

(6) the deprotection reaction using a metal complex is carried out, for example, in an organic solvent (dichloromethane, dimethylformamide, tetrahydrofuran, ethyl acetate, acetonitrile, dioxane, ethanol, etc.), water or a mixture thereof, in the presence of a trap reagent (tributyltin hydride, triethylsilane, dimedone, morpholine, diethylamine, pyrrolidine, etc.), an organic acid (acetic acid, formic acid, 2-ethylhexane, etc.) and/or a salt of an organic acid (sodium 2-ethylhexanoate, potassium 2-ethylhexanoate, etc.) in the presence or absence of a phosphine reagent (triphenylphosphine etc.) using a metal complex (palladium tetrakistriphenylphosphine (0), palladium bis(triphenylphosphosphine) dichloride (II), palladium acetate (II), rhodium tris(triphenylphosphine) chloride (I), etc. at a temperature of 0 to 40°C.

In addition to the above, deprotection reaction may be carried out by the method, for example, described in T. W. Greene, Protective Groups in Organic Synthesis, Wiley, New York, 1999.

Protective groups for carboxy include, for example, methyl, ethyl, allyl, tert-butyl, trichloroethyl, benzyl (Bn), phenacyl, p-methoxybenzyl, trityl, 2-chlorotrityl or a solid carrier containing these structure, etc.

Protective groups for hydroxy include, for example, methyl, trityl, methoxymethyl (MOM), 1-ethoxyethyl (EE), methoxyethoxymethyl (MEM), 2-tetrahydropyranyl (THP), trimethylsilyl (TMS), triethylsilyl (TES), tert-butyldimethylsilyl (TBDMS), tert-butyldiphenylsilyl (TBDPS), acetyl (Ac), pivaolyl, benzoyl, benzyl (Bn), p-methoxybenzyl, allyloxycarbonyl (Alloc) or 2,2,2-trichloroethoxycarbonyl (Troc), etc.

Protective groups for amino include, for example, benzyloxycarbonyl, tert-butoxycarbonyl,

allyloxycarbonyl (Alloc), 1-methyl-1-(4-biphenyl)ethoxycarbonyl (Bpoc), trifluoroacetyl, 9-fluorenylmethoxycarbonyl, benzyl (Bn), p-methoxybenzyl or benzyloxymethyl (BOM), 2-(trimethylsilyl)ethoxymethyl (SEM), etc.

Protective groups for thiol include, for example, benzyl, methoxybenzyl, methoxymethyl (MOM), 2-tetrahydropyranyl (THP), diphenylmethyl, acetyl (Ac), etc.

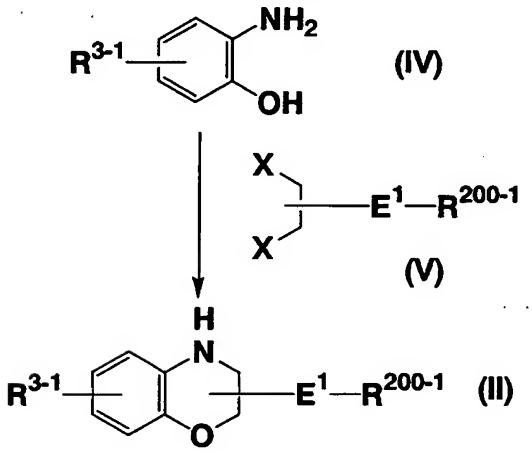
The protective groups for tetrazolyl include, for example, tert-butyl, methyloxycarbonyl, benzyloxycarbonyl, tert-butoxycarbonyl, allyloxycarbonyl (Alloc), 1-methyl-1-(4-biphenyl)ethoxycarbonyl (Bpoc), trifluoroacetyl, 9-fluorenylmethoxycarbonyl, benzyl (Bn), α,α-dimethylbenzyl, trityl, p-methoxybenzyl, benzyloxymethyl (BOM), 2-(trimethylsilyl)ethoxymethyl (SEM), trimethylsilyl (TMS), triethylsilyl (TES) or 2-cyanoethyl, etc.

Protective groups for carboxy, hydroxy, amino, thiol or tetrazolyl are not limited to the above ones, but those groups which are easily and selectively eliminated are also acceptable. For example, those groups described in T. W. Greene, Protective Groups in Organic Synthesis, Wiley, New York, 1999 are used.

As is easily understood by those skilled in the art, the target compound of the present invention may be prepared easily by selecting these deprotection reactions.

The compound of formula (II) may be prepared by the method described in the reaction scheme 1. In these reaction schemes, all symbols have the same meaning as described hereinbefore.

Reaction Scheme 1



The compounds of formula (III), (III-1), (III-2), (IV) and (V), which are used as starting materials or reagents, are known per se, or may be easily prepared by known methods, e.g. described in "Comprehensive Organic Transformations:A Guide to Functional Group Preparations 2nd Edition (Richard C. Larock, John Wiley & Sons Inc, 1999)".

Among the compounds of formula (I) of the present invention, the compounds other than those

described above may be prepared by combining the methods described in the examples of the present specification and/or known methods, e.g. described in "Comprehensive Organic Transformations:A Guide to Functional Group Preparations 2nd Edition(Richard C. Larock, John Wiley & Sons Inc, 1999)".

In each reaction of the present specification, the reactions accompanied by heating, as is obvious to those skilled in the art, may be carried out in a water bath, an oil bath, a sand bath or they may be carried out using a microwave.

In each reaction of the present specification, if required, reagents which are supported with high molecular polymers (e.g. polystyrene, polyacrylamide, polypropylene, polyethyleneglycol, etc.) may also be used.

In each reaction of the present specification, reaction products may be purified by conventional techniques, e.g. distillation under atmospheric or reduced pressure, high performance liquid chromatography, thin layer chromatography or ion exchange chromatography using silica gel or magnesium silicate, washing, recrystallization, etc. Purification may be carried out after each reaction, or after a series of reactions.

In the present invention, as is easily understood by those skilled in the art, the symbol

indicates that the substituent attached thereto is behind the sheet (i.e. α-position), the symbol

indicates that the substituent attached thereto is in front of the sheet (i.e. β-position), and the symbol

indicates that the substituent attached thereto is in α-position, β-position, or a mixture thereof, and the symbol

indicates that the substituent attached thereto is a mixture of the compounds in α-position or β-position.

Unless otherwise specified, all isomers are included in the present invention. For example, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylene, alkenylene or alkynylene group includes straight or branched ones. In addition, isomers on double bonds, rings, fused rings (E-, Z-, cis-, trans-isomer), isomers generated from asymmetric carbon atom(s) (R-, S-, α-, β-isomer, enantiomer, diastereomer), optically active isomers having optical activity (D-, L-, d-, l-isomer), tautomers, polar compounds generated by chromatographic separation (more polar compounds, less polar compounds), equilibrium compounds, rotational isomers, mixtures thereof at optional ratios and racemic mixtures are also included in the present invention.

The compound of formula (I) is converted to salts by known methods. The salts are preferabley

pharmaceutically acceptable ones.

The salts include salts of alkali metals, salts of alkaline earth metals, ammonium salts, amine salts, acid addition salt etc.

The salts are preferably water-soluble ones. Appropriate salts include, for example, salts of alkali metals (potassium, sodium, etc.), salts of alkaline earth metals (calcium, magnesium, etc.), ammonium salts, pharmaceutical acceptable organic amine salts (triethylamine, methylamine, dimethylamine, cyclopentylamine, benzylamine, phenethylamine, piperidine, monoethanolamine, diethanolamine, tris(hydroxymethyl)methylamine, lysine, arginine, N-methyl-D-glucamine, etc.).

The acid addition salts are preferably water-soluble ones. Appropriate acid addition salts include, for example, hydrochloride, hydrobromide, hydroiodide, sulfate, phosphate, nitrate, etc.; organic acid salts such as acetate, trifluoroacetate, lactate, tartrate, oxalate, fumarate, maleate, benzoate, citrate, methanesulfonate, ethanesulfonate, benzenesulfonate, toluenesulfonate, isethionate, glucuronate, gluconate, etc.

The compound of formula (I) and the salt thereof is also converted to solvate.

The solvate is preferably non-toxic and water-soluble. Appropriate solvate includes, for example, water, or alcohol solvents (ethanol etc.).

The toxicity of the compound of formula (I) is very low for pharmaceutical use.

The compound of formula (I), a pharmaceutically acceptable salt thereof, or a solvate thereof antagonizes cysLT$_2$ receptor, and therefore, it is useful as an inhibitor of airway contraction, inhibitor of infiltration of inflammatory cells (e.g. eosinophils, neutrophils, lymphocytes, basophils, etc.), an inhibitor of mucus secretion or an inhibitor of increased airway hyperreactivity. Also, the compound of formula (I), a salt thereof, or a solvate thereof is useful for the prevention and/or treatment of those diseases in which cysLT$_2$ receptor is involved, for example, respiratory diseases (e.g. bronchial asthma, chronic obstructive pulmonary diseases, lung emphysema, chronic bronchitis, pneumonia including interstitial pneumonitis, etc.), severe acute respiratory syndrome (SARS), acute respiratory distress syndrome (ARDS), allergic rhinitis, sinusitis including acute sinusitis, chronic sinusitis, etc., and the like), and as an expectorant or an antitussive agent. Furthermore, the compound of formula (I) of the present invention, a salt thereof, or a solvate thereof is useful as an agent for the improvement of respiratory functions.

The respiratory function is defined as, e.g. the function of taking air in and out (i.e. function of pulmonary capacity), the function of taking oxygen from lungs into blood and taking carbon dioxide from blood out of the body (i.e. function of oxygen exchange), and the function of respiratory resistance.

In the present invention, respiratory apparatus means the body part involved in respiration,

such as airway, oral cavity, nasal cavity, nasal sinuses, trachea, bronchial tube, bronchiole, lung, etc.

In the present invention, non-responders are defined as those patients to whom existing LT receptor antagonists give insufficient effect or no effect. Since the agent for the treatment of the present invention is more useful for respiratory diseases than an existing LT receptor antagonist, it is preferable to administer it to non-responders and those patients with severe disorders in respiratory functions (e.g. severe bronchial asthma patients).

In the present invention, the measuring method of IC_{50} values or Ki values of antagonizing effect against $cysLT_2$ receptor is not limited in particular, and it may be carried out by known methods. For example, it may be carried out according to the methods described in J. Biol. Chem., 275, 30531-30536, (2000), Mol. Pharmacol., 58, 1601-1608, (2000), or Biochem. Biophys. Res. Commun., 274, 316-322, (2000), etc.

In the present invention, the compound of formula (I) may have an antagonizing effect against $cysLT_1$ receptor.

The $cysLT_2$ receptor antagonists may be in the form of a prodrug of the compound of formula (I).

The prodrugs of the compound of formula (I) are, when the compound of formula (I) possesses an amino group, the amino group is acylated, alkylated, phosphorylated (e.g. the amino group of the compound of formula (I) is eicosanoylated, alanylated, pentylaminocarbonylated, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxycarbonylated, tetrahydrofuranylated, pyrrolidylmethylated, pivaloyloxymethylated, acetoxymethylated, t-butylated, etc.); when the compound of formula (I) possesses a hydroxy group, the hydroxy group is acylated, alkylated, phosphorylated, borated (e.g. the hydroxy group of the compound of formula (I) is acetylated, palmitoylated, propanoylated, pivaloylated, succinylated, fumarylated, alanylated, dimethylaminomethylcarbonylated, etc.); when the compound of formula (I) possesses a carboxy group, the carboxy group is esterified, or amidated (e.g. the carboxy group of the compound of formula (I) is converted into ethyl ester, phenyl ester, carboxymethyl ester, dimethylaminomethyl ester, pivaloyloxymethyl ester, ethoxycarbonyloxyethyl ester, phthalidyl ester, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl ester, cyclohexylcarbonylethyl ester, methyl amide, etc.), etc. These compounds may be prepared by known methods. The prodrug of the compound (I) may be a hydrate or a non-hydrate.

The compound of formula (I), a pharmaceutically acceptable salt thereof, a solvate thereof or a prodrug thereof may be administered in combination with other agents for the purpose of (1) supplementing and/or reinforcement of preventive and/or treating effect, (2) improvement in kinetics and absorption and reduction of dose, and/or (3) reduction of side effect, of the agent for the treatment of the present invention.

Concomitant agents of the agent for the treatment of the present invention with other agents may be administered in a mode of an agent in which both components are compounded in a single preparation or in a mode of separate preparations. When administration is conducted using separate preparations, a simultaneous administration and administrations with time difference are included. In the case of administrations with time difference, the agent for the treatment of the present invention may be firstly administered and then the other drug may be administered, and vice versa. Each of the methods for the administration may be the same or different.

The other agents as described above may be low molecular compounds, high molecular protein, polypeptides, polynucleotides (DNA, RNA, genes), anti-sense, decoy, antibody, vaccines, etc. The dose of the other agents may be determined taking the clinically used dose as a reference appropriately. The ratio of the agent for the treatment of the present invention and the other agents may be determined according to the age, weight, route of administration, time of administration, the target disease, symptom or combination, etc. For example, approximately 0.01 to 100 of the other agents in weight ratio may be used versus the agent for the treatment of the present invention. One or more of the other agent(s) may be selected from the same group or different groups described hereafter, and may be administered alone or in combination thereof in optional ratios. The other agents which supplement and/or reinforce the preventing and/or treating effect of the agent for the reatment of the present invention include not only those have been found out so far, but also those are to be found out from now on, based on the above mechanism.

The diseases on which the concomitant agents show the preventing and/or treating effect are not limited in particular, and those diseases in which the preventing and/or treating effect of the agent of the present invention are supplemented and/or reinforced are included.

For example, the other agents for supplement and/or reinforcement of the preventing and/or treating effect of the agent of the present invention against respiratory diseases include, for example, cysLT$_1$ receptor antagonists, antihistamine agents, antiallergic agents (e.g. chemical mediator release inhibitors, histamine antagonists, thromboxane synthase inhibitors, thromboxane antagonists, Th$_2$ cytokine inhibitors), steroidal agents, bronchodilating agents (e.g. xanthine derivatives, sympathomimetic agents, parasympatholytic agents), vaccine therapy agents, gold formulations, Chinese medicines, basic non-steroidal antiinflammatory agents, 5-lipoxygenase inhibitors, 5-lipoxygenase activated protein antagonists, leukotriene synthesis inhibitors, prostaglandin agents, cannabinoid-2 receptor agonists, antitussive agents, expectorant agents or extract from inflammatory rabbit skin inoculated by vaccinia virus, etc.

CysLT$_1$ receptor antagonists include, for example, pranlukast hydrate, montelukast sodium, zafirlukast, MK-571, LY-203647, WY-46016, WY-48422, WY-49353, WY-49451, RG-12553,

MDL-43291, CGP-44044A, RG-14524, LY-287192, LY-290324, L-695499, RPR-105735B, WAY-125007, OT-4003, LM-1376, LY-290154, SR-2566, L-740515, LM-1453, CP-195494, LM-1484, CR-3465, ablukast, pobilukast, sulukast, L-648051, RG-12525, RG-7152, SK&F-106203, SR-2640, WY-50295, iralukast sodium, verlukast, MCC-847, BAY-x-7195, ritolukast, cinalukast, CGP-44826, FK-011, YM-158, MEN-91507, KCA-757, RS-601, RS-635, S-36496, ZD-3523, DS-4574, pirodomast, AS-35, YM-57158, MCI826, NZ-107, 4414-CERM, YM-16638, Wy-48252, Wy-44329, Wy-48090, VUF-4679, tomelukast, SM-11044, SC-39070, OT-3473, N-2401, LY-243364, L-649923, doqualast, DP-1934, YM-17551, Wy-47120, VUF-K-8707, SK&F-88046, SK&F-101132, SK&F-102922, LY-137617, LY-163443, LY-302905, L-647438, L-708738, KY-234, FPL-55712, CP-288886, S-36527, CGP-35949, CS-615, MDL-19301D, SCH-40120, ZD-3705, etc.

$CysLT_1$ receptor antagonists are preferably, pranlukast hydrate, montelukast sodium, zafirlukast or MK-571, more preferably, pranlukast hydrate, montelukast sodium or zafirlukast.

Antihistamine agents include, for example, diphenhydramine hydrochloride, diphenylpyraline hydrochloride, diphenylpyraline chlorotheophyllinate, clemastine fumarate, dimenhydrinate, dl-chlorpheniramine maleate, d-chlorpheniramine maleate, triprolidine hydrochloride, promethazine hydrochloride, alimemazine tartrate, isothipendyl hydrochloride, homochlorcyclizine hydrochloride, hydroxyzine, cyproheptadine hydrochloride, levocabastine hydrochloride, astemizole, bepotastine, desloratadine, TAK-427, ZCR-2060, NIP-530, mometasone furoate, mizolastine, BP-294, andolast, auranofin, acrivastine, etc.

Among the antiallergic agents, chemical mediator release inhibitors include, for example, sodium cromoglicate, tranilast, anlexanox, repirinast, ibudilast, potassium pemilolast, tazanolast, nedocromil, cromoglicate, israpafant, etc.

Among the antiallergic agents, histamine antagonists include, for example, ketotifen fumarate, azelastine hydrochloride, oxatomide, mequitazine, terfenadine, emedastine difumarate, epinastine hydrochloride, ebastin, cetirizine hydrochloride, olopatadine hydrochloride, loratadine, fexofenadine, etc.

Among the antiallergic agents, thromboxane synthase inhibitors include, for example, ozagrel hydrochloride or imitrodast sodium, etc.

Among the antiallergic agents, thromboxane antagonists are, for example, seratrodast, ramatoroban, domitroban calcium hydrate, KT-2-962, etc.

Among the antiallergic agents, TH2 cytokine inhibitors include, for example, suplatast tosylate, etc.

Steroidal agents as external medicines include, for example, clobetasol propionate, diflorasone acetate, fluocinonide, mometasone furoate, betamethasone dipropionate, betamethasone butyrate propionate, betamethasone valerate, difluprednate, budesonide, diflucortolone valerate,

amcinonide, halcinonide, dexamethasone, dexamethasone propionate, dexamethasone valerate, dexamethasone acetate, hydrocortisone acetate, hydrocortisone butyrate, hydrocortisone butyrate propionate, deprodone propionate, prednisolone valerate acetate, fluocinolone acetonide, beclomethasone dipropionate, triamcinolone acetonide, flumethasone pivalate, alclometasone dipropionate, clobetasone butyrate, prednisolone, beclomethasone dipropionate, fludroxycortide, etc. Internal medicines and injections include, for example, cortisone acetate, hydrocortisone, sodium hydrocortisone phosphate, sodium hydrocortisone succinate, fludrocortisone acetate, prednisolone, prednisolone acetate, sodium prednisolone succinate, butyl prednisolone acetate, prednisolone sodium phosphate, halopredone acetate, methyl prednisolone, methyl prednisolone acetate, sodium methyl prednisolone succinate, triamcinolone, triamcinolone acetate, triamcinolone acetonide, dexamethasone, dexamethasone acetate, sodium dexamethasone phosphate, dexamethasone palmitate, paramethasone acetate, betamethasone, etc. Inhalant medicines include, for example, beclometasone dipropionate, fluticasone propionate, budesonide, flunisolide, triamcinolone, ST-126P, ciclesonide, dexamethasone paromitionate, mometasone furoate, prasterone sulfonate, deflazacort, methylprednisolone, sleptanate, methylprednisolone sodium succinate, etc.

Among the bronchodilating agents, the xanthine derivatives include, for example, aminophylline, theophylline, doxophylline, cipamphilline, diprophilline, proxyphylline, choline theophylline, etc.

Among the bronchodilating agents, sympathomimetic agents include, for example, epinephrine, ephedrine hydrochloride, dl-methylephedrine hydrochloride, methoxyphenamine hydrochloride, isoproterenol sulfate, isoproterenol hydrochloride, orciprenaline sulfate, clorprenaline hydrochloride, trimetoquinol hydrochloride, salbutamol sulfate, terbutaline sulfate, hexoprenaline sulfate, tulobuterol hydrochloride, procaterol hydrochloride, fenoterol hydrobromide, formoterol fumarate, clenbuterol hydrochloride, mabuterol hydrochloride, salmeterol xinafoate, R,R-formoterol, tulobuterol, pirbuterol hydrochloride, ritodrine hydrochloride, bambuterol, dopexamine hydrochloride, meluadrine tartrate, AR-C68397, levosalbutamol, KUR-1246, KUL-7211, AR-C89855, S-1319, etc.

Among the bronchodilating agents, parasympatholytic agents include, for example, ipratropium bromide, flutropium bromide, oxitropium bromide, cimetropium bromide, temiverine, tiotropium bromide, revatropate (UK-112166), etc.

Vaccine therapy agents include, for example, paspat, astremesin, broncasma berna, CS-560, etc.

Gold formulations include, for example, gold sodium thiomalate etc.

Basic non-steroidal antiinflammatory agents include, for example, tiaramide hydrochloride, tinoridine hydrochloride, epirizole, emorfazone, etc.

5-lipoxygenase inhibitors include, for example, diruton, docebenone, piripost, SCH-40120, WY-50295, E-6700, ML-3000, TMK-688, ZD-2138, darbufelone mesylate, R-68151, E-6080, DuP-654, SC-45662, CV-6504, NE-11740, CMI-977, NC-2000, E-3040, PD-136095, CMI-392, TZI-41078, Orf-20485, IDB-18024, BF-389, A-78773, TA-270, FLM-5011, CGS-23885, A-79175 or ETH-615, etc.

5-lipoxygenase activating protein antagonists include, for example, MK-591 or MK-886, etc.

Leukotriene synthase inhibitors include, for example, auranofin, proglumetacin maleate, L-674636, A-81834, UPA-780, A-93178, MK-886, REV-5901A, SCH-40120, MK-591, Bay-x-1005, Bay-y-1015, DTI-0026, amlexanox or E-6700, etc.

Prostaglandins (abbreviated as PG hereafter) include, for example, PG receptor agonist, PG receptor antagonist, etc.

PG receptors include, for example, PGE receptor (EP_1, EP_2, EP_3, EP_4), PGD receptor (DP, $CRTH_2$), PGF receptor (FP) or PGI receptor (IP), TX receptor (TP), etc.

Antitussive agents include, for example, codeine phosphate, dihydrocodeine phosphate, dextromethorphan hydrobromide, pentoxyverine citrate, dimemorfan phosphate, oxeladin citrate, chloperastine, benproperine phosphate, clofedanol hydrochloride, fominoben hydrochloride, noscapine, tipepidine hibenzate, eprazinone hydrochloride, plantago, etc.

Expectorants include, for example, fennel ammonium spirit, sodium bicarbonate, potassium iodide, bromhexine hydrochloride, cherry bark extract, carbocysteine, fudostein, ambroxol hydrochloride, ambroxol hydrochloride extended release drug, methylcysteine hydrochloride, acetylcysteine, L-ethylcycteine hydrochloride, cysteine, tyloxapol, etc.

The other agents to be used in combination with the compound of the present invention are preferably, $cysLT_1$ receptor antagonists, steroidal agents or sympathomimetics.

The formulation to be used in the present invention may contain the $cysLT_2$ receptor antagonists and the other agent(s) supplementing and/or reinforcing the treating effect of the compound which are compounded in a single preparation or in separate preparations. These are formulated by known methods.

The formulation is administered normally systemically or topically, orally or parenterally, for the purpose of the present invention.

The dosages are determined depending on age, body weight, symptom, therapeutic effect, administration route, duration of the treatment and the like. Generally, for an adult, approximately 1 mg to 1000 mg per dose is orally administered once to several times per day, or approximately 1 mg to 100 mg is parenterally administered once to several times per day, or continuously administered from vein for 1 to 24 hours per day.

As described hereinbefore, since the dosage changes depending on various conditions as described above, there are cases in which doses lower than or greater than the above ranges may

be used.

The compound is administered in the form of solid compositions for oral administration or liquid compositions for oral administration, or injectable compositions, external medicine, suppositories, eye lotions, inhalants and the like for parenteral administration, for the purpose of the present invention.

The solid formulations for oral administration include, for example, tablets, pills, capsules, powdered drugs, granulated drugs, etc.

Capsules include hard capsules and soft capsules.

In such solid formulations, said one or more active agent(s) are formulated according to usual methods as it is, or mixed with one or more of an excipient (lactose, mannitol, glucose, microcrystalline cellulose, starch, etc.), a binding agent (hydroxypropyl cellulose, polyvinylpyrrolidone, magnesium aluminometasilicate, etc.), a disintegrating agent (calcium glycolate cellulose, carmellose, starch, crystalline cellulose, etc.), a lubricant (magnesium stearate etc.), a stabilizing agent or a solubilizing agent (glutamic acid, aspartic acid, etc.), etc. If necessary, the formulations may be coated with a coating agent such as sugar, gelatin, hydroxypropyl cellulose, hydroxypropylmethyl cellulose phthalate, or may be coated with two or more layers thereof. Alternatively, the solid agent may be capsulized by an absorbable material such as gelatin.

The liquid formulations for oral administration include pharmaceutically acceptable aqueous solution, suspension, emulsion, syrup, elixir, etc. In such liquid formulations, one or more of the active agent(s) are dissolved, suspended or emulsified in a commonly used diluent (e.g., purified water, ethanol, or a mixture thereof). Furthermore, such liquid formulations may comprise a wetting agent, a suspending agent), an emulsifier, a sweetening agent, a flavoring agent, an aromatic agent, a preservative, a buffer etc.

Injectable formulations for parenteral administration include, for example, a solution, a suspension, an emulsion or solid formulation for injection which is dissolved or suspended in use. The injectable formulation is prepared by dissolving, suspending or emulsifying one or more of active substance in a solubilizing agent. The solubilizing agents include, for example, distilled water for injection, saline, vegetable oil, propylene glycol, polyethyleneglycol or alcohols such as ethanol, and a combination thereof. The injectable formulation may further contain a stabilizing agent, a solubilizing agent (glutamic acid, aspartic acid, polysorbate 80 (trade name), etc.), a suspending agent, emulsifying agent, a soothing agent, a tonicity agent, a buffer, or a preservative, etc. These are sterilized in the final step or are prepared by aseptic manipulation. Sterile solid formulation, such as freeze-dried formulation, may be prepared, to sterilize or to solve in sterile distilled water for injection or other sterile solvents before use.

The eye drops for parenteral administration may be in the form of liquid eye drops, suspended

eye drops, emulsified eye drops or eyedrops which is used by dissolving in a solvent in use or eye ointment.

These eye drops are prepared by known methods. For example, in the case of liquid eye drops, they may be prepared by appropriately selecting and comprising one or more agent(s) such as an isotonic agent (sodium chloride, concentrated glycerin, etc.), a buffer (sodium phosphate, sodium acetate, etc.), a surface active agent (Polysolvate 80 (trade name), polyoxyl stearate 40, polyoxyethylene-hardened castor oil, etc.), a stabilizer (sodium citrate, sodium edentate, etc.), and a preservative (benzalconium chloride, paraben, etc.), and the like. depending on the needs. The eye drops are sterilized at the final step or prepared by an aseptic process.

The inhalable formulation for parenteral administration may be in the form of aerosol, inhalable powder or inhalable liquid formulation. The inhalable liquid formulation may be dissolved or suspended in water or other appropriate medium in use.

These inhalable formulations may be prepared according to known methods.

For example, inhalable liquid formulations may further contain antiseptics (benzalkonium chloride, paraben, etc.), a coloring agent, a buffer (sodium phosphate, sodium acetate, etc.), a tonicity agent (sodium chloride, concentrated glycerine, etc.), a thickening agent (carboxyvinyl polymer, etc.), an absorption promoter, and the like.

Inhalable powders may be prepared by appropriately selecting and comprising one or more agent(s) such as a lubricant (stearic acid, a salt thereof, etc.), a binding agent (starch, dextrin, etc.), an excipient (lactose, cellulose, etc.), a coloring agent, an antiseptic agent (benzalchonium chloride, parabens, etc.), an absorption promoter, and the like.

Inhalable liquid formulations may normally be administered by sprayer (e.g. atomizer, nebulizer, etc.) and inhalable powders may be administered by using inhalers for powder formulations.

The other compositions for parenteral administration include a liquid preparation for external application, an ointment, a liniment, a spray formulation, a suppository, a pessary for intravaginal administration, and the like.

The spray formulation may include, besides generally used diluents, a stabilizing agent (sodium hydrogensulfite, sodium citrate, sodium edetate, etc.), a buffert (e.g. sodium citrate, citric acid, sodium acetate, sodium hydrogenphosphate, boric acid, borax, etc.), a tonicity agent (e.g. sodium chloride, glycerine, concentrated glycerine, mannitol, etc.), and the like. For the preparation of the spray formulation, for example, the methods described in the United States Patent No. 2,868,691 and ibid. 3,095,355 may be used.

[Effect of the Invention]

The compound of formula (I), a salt thereof, or a solvate thereof antagonizes cysLT$_2$ receptor,

and therefore, it is useful as an inhibitor of airway contraction, inhibitor of infiltration of inflammatory cells (e.g. eosinophils, neutrophils, lymphocytes, basophils, etc.), an inhibitor of mucus secretion or an inhibitor of increased airway hyperreactivity. Also, the compound of formula (I), a salt thereof, or a solvate thereof is useful for the prevention and/or treatment of those diseases in which $cysLT_2$ receptor is involved, for example, respiratory diseases (e.g. bronchial asthma, chronic obstructive pulmonary diseases, lung emphysema, chronic bronchitis, pneumonia including interstitial pneumonitis, etc.), severe acute respiratory syndrome (SARS), acute respiratory distress syndrome (ARDS), allergic rhinitis, sinusitis including acute sinusitis, chronic sinusitis, etc., and the like), and as an expectorant or an antitussive agent. Furthermore, the compound of formula (I) of the present invention, a salt thereof, a solvate thereof is useful as an agent for the improvement of respiratory functions.

[Best Mode for Carrying out the Invention]

The present invention is illustrated by the following Examples and biological Examples, but it is not limited thereto.

The solvents in the parentheses described in chromatography separation and TLC show the eluting or developing solvents, and the ratios of the solvents used are by volume in chromatographic separations or TLC. NMR means ^{1}H-NMR and the solvents in the parentheses in NMR show the solvents used in measurement.

The nomenclature in the present invention was carried out according to ACD/Name (Version 6.00; Advanced Chemistry Development Inc.).

Example 1: 2-(benzyloxy)-3-nitrobenzoic acid

To a solution of 2-hydroxy-3-nitrobenzoic acid (36.6 g) in N,N-dimethylformamide (500 mL) were added benzyl bromide (50.0 mL) and potassium carbonate (66.3 g), and the mixture was stirred overnight at 60°C. The reaction mixture was poured into water and the resulting mixture was extracted with a mixture of ethyl acetate and n-hexane (1 : 1). The organic layer was washed with water and saturated brine, dried over anhydrous sodium sulfate and concentrated. The residue was dissolved in a mixture of tetrahydrofuran (100 mL) and methanol (200 mL), and the resulting mixture was stirred for 30 minutes at 50°C. The reaction mixture was concentrated and the residue was acidified with 2N hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous sodium sulfate and concentrated. The residue was recrystallized from isopropanol (50 mL)/n-hexane (200 mL) to give the title compound (31.99 g) having the following physical data.

TLC: Rf 0.43 (methylene chloride : methanol : acetic acid = 19 : 1 : 0.1).

Example 2: tert-butyl (2-(benzyloxy)-3-nitrophenyl)carbamate

To a solution of the compound prepared in Example 1 (30.0 g) and triethylamine (16.2 mL) in

toluene (440 mL) was added diphenylphosphorylazide (24.9 mL) dropwise at room temperature. The reaction mixture was stirred for 2 hours at 80°C. To the reaction mixture was added tert-butanol (52.6 mL) and the mixture was stirred for 3 hours at 80°C. The reaction mixture was cooled down to room temperature, washed successively with water, 0.1N hydrochloric acid, water, saturated aqueous sodium bicarbonate solution and saturated brine, dried over sodium sulfate and concentrated. The residue was purified by column chromatography on silica gel (n-hexane : ethyl acetate = 9 : 1) to give the title compound (32.98 g) having the following physical data.

TLC: Rf 0.40 (n-hexane : ethyl acetate = 9 : 1).

Example 3: (2-(benzyloxy)-3-nitrophenyl)amine hydrochloride

To the compound prepared in Example 2 (20.66 g) was added 4N hydrochloric acid solution in dioxane (120 mL), and the mixture was stirred overnight at room temperature. To the reaction mixture was added n-hexane (120 mL), and the resulting mixture was stirred for 1 hour with ice cooling. The resulting solid was collected by filtration, and it was washed with ethyl acetate to give the title compound (15.2 g) having the following physical data.

TLC: Rf 0.40(n-hexane : ethyl acetate = 2 : 1).

Example 4: N-(2-(benzyloxy)-3-nitrophenyl)-4-(4-phenylbutoxy)benzamide

To a suspension of 4-(4-phenylbutoxy)benzoic acid (5.40 g) in methylene chloride (20 mL) were added oxalyl chloride (2.09 mL) and N,N-dimethylformamide (1 drop), and the resulting mixture was stirred for 2 hours at room temperature and then concentrated. To a suspension of the compound prepared in Example 3 (5.61 g) in methylene chloride (60 mL) were added pyridine (4.85 mL) and the previously prepared acid chloride in methylene chloride (20 mL), with ice cooling and the resulting mixture was stirred for 3 hours at room temperature. The reaction mixture was concentrated and the residue was diluted with ethyl acetate. The diluted solution was washed sequentially with water, 1N hydrochloric acid, water, saturated aqueous sodium bicarbonate solution and saturated brine, dried over anhydrous sodium sulfate and concentrated. The residue was recrystallized from a mixed solvent of ethyl acetate (100 mL) and n-hexane (100 mL) to give the title compound (8.58 g) having the following physical data.

TLC: Rf 0.54 (n-hexane : ethyl acetate = 2 : 1).

Example 5: N-(3-amino-2-hydroxyphenyl)-4-(4-phenylbutoxy)benzamide

A mixture of the compound prepared in Example 4 (8.58 g), 10% palladium-carbon (429 mg), tetrahydrofuran (60 mL) and methanol (30 mL) was stirred for 5.5 hours under atmosphere of hydrogen. The catalyst was filtered off and the filtrate was concentrated. The residue was recrystalized from a mixed solvent of isopropanol (13 mL) and n-hexane (52 mL) to give the title compound (6.07 g) having the following physical data.

TLC: Rf 0.46 (n-hexane : ethyl acetate = 1 : 1).

Example 6:

ethyl 8-((4-(4-phenylbutoxy)benzoyl)amino)-3,4-dihydro-2H-1,4-benzoxazine-2-carboxylate

To a solution of the compound prepared in Example 5 (3.76 g) in acetone (40 mL) were added potassium carbonate (4.15 g) and ethyl 2,3-dibromopropionate (1.74 mL), and the mixture was stirred overnight at 50°C. The reaction mixture was concentrated and the residue was diluted with ethyl acetate. The diluted solution was washed with water and saturated brine sequentially, dried over anhydrous sodium sulfate and concentrated. The residue was purified by column chromatography on silica gel (n-hexane : ethyl acetate = (4 : 1) to (2 : 1)) to give the title compound (3.51 g) having the following physical data.

TLC: Rf 0.48(n-hexane : ethyl acetate = 1 : 1).

Example 7:

ethyl

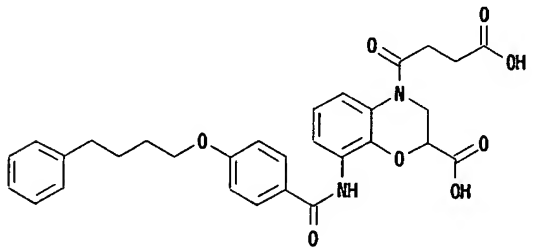
4-(4-methoxy-4-oxobutanoyl)-8-((4-(4-phenylbutoxy)benzoyl)amino)-3,4-dihydro-2H-1,4-benzoxazine-2-carboxylate

To a solution of the compound prepared in Example 6 (776 mg) in pyridine (5 mL) was added 3-(carbomethoxy)propionyl chloride (302 μL), and the mixture was stirred for 1 hour at room temperature. The reaction mixture was poured into water and the resulting mixture was extracted with ethyl acetate. The organic layer was washed sequentially with 1N hydrochloric acid, water, saturated aqueous sodium bicarbonate solution and saturated brine, dried over anhydrous sodium sulfate and concentrated. The residue was recrystallized from a mixed solvent of ethyl acetate (5 mL) and n-hexane (5 mL) to give the title compound (711 mg) having the following physical data.

TLC: Rf 0.38(n-hexane : ethyl acetate = 1 : 1).

Example 8:

4-(3-carboxypropanoyl)-8-((4-(4-phenylbutoxy)benzoyl)amino)-3,4-dihydro-2H-1,4-benzoxazine-2-carboxylic acid



To a mixture of the compound prepared in Example 7 (700 mg), tetrahydrofuran (2 mL) and ethanol (2 mL) was added 2N aqueous solution of sodium hydroxide (2 mL), and the mixture was stirred for 1 hour at room temperature. The reaction mixture was acidified with 2N hydrochloric acid and extracted with ethyl acetate. The organic layer was washed sequentially

with water and saturated brine, dried over anhydrous sodium sulfate and concentrated. The residue was recrystallized from ethanol to give the compound of the present invention (486 mg) having the following physical data.

TLC: Rf 0.21 (methylene chloride : methanol : acetic acid = 90 : 10 : 1);

^{1}H-NMR(CD_3CO_2D): δ 1.73-1.92, 2.60-2.97, 2.98-3.14, 4.05-4.22, 4.38, 5.19, 6.97-7.06, 7.11-7.30, 7.90-7.98, 8.13.

Example 8(1) - Example 8(4)

The compounds of the present invention having the following physical data were prepared by using corresponding hydroxynitrobenzoic acids instead of 2-hydroxy-3-nitrobenzoic acid, and using corresponding acid chlorides in stead of 3-(carbomethoxy)propionyl chloride in the process of Example 1→Example 2→Example 3→Example 4→Example 5→Example 6→Example 7→Example 8.

Example 8(1):

4-(4-carboxybutanoyl)-8-((4-(4-phenylbutoxy)benzoyl)amino)-3,4-dihydro-2H-1,4-benzoxazine-2-carboxylic acid

TLC: Rf 0.25 (methylene chloride : methanol : acetic acid = 90 : 10 : 1);

^{1}H-NMR(DMSO-d_6): δ 1.74, 2.24, 2.64, 3.69, 4.07, 4.47, 5.15, 6.92, 7.03, 7.21, 7.67, 7.91, 9.30, 12.06.

Example 8(2):

4-(5-carboxypentanoyl)-8-((4-(4-phenylbutoxy)benzoyl)amino)-3,4-dihydro-2H-1,4-benzoxazine-2-carboxylic acid

TLC: Rf 0.32 (methylene chloride : methanol : acetic acid = 90 : 10 : 1);

^{1}H-NMR(DMSO-d_6): δ 1.53, 1.72, 2.20, 2.60, 3.67, 4.07, 4.48, 5.14, 6.91, 7.03, 7.21, 7.66, 7.91, 9.29, 12.71.

Example 8(3):

4-(3-carboxypropanoyl)-6-((4-(4-phenylbutoxy)benzoyl)amino)-3,4-dihydro-2H-1,4-benzoxazine-2-carboxylic acid

TLC: Rf 0.26 (methylene chloride : methanol : acetic acid = 40 : 10 : 1);

^{1}H-NMR(CD_3CO_2D): δ 1.72-1.92, 2.61-2.84, 2.85-3.02, 3.01-3.23, 3.95, 4.07, 4.42-4.61, 5.06, 6.94-7.07, 7.11-7.33, 7.36-7.77, 7.77-8.29.

Example 8(4):

4-(3-carboxypropanoyl)-7-((4-(4-phenylbutoxy)benzoyl)amino)-3,4-dihydro-2H-1,4-benzoxazine-2-carboxylic acid

TLC: Rf 0.25 (methylene chloride : methanol : acetic acid = 40 : 10 : 1);

^{1}H-NMR(CD_3CO_2D): δ 1.73-1.91, 2.60-2.96, 2.96-3.17, 3.93, 4.07, 4.42-4.64, 4.97-5.15, 6.95-7.03, 7.10-7.63, 7.89-7.98.

Example 9:

8-((4-(4-phenylbutoxy)benzoyl)amino)-3,4-dihydro-2H-1,4-benzoxazine-2-carboxamide

To a solution of the compound prepared in Example 6 (1.80 g) in ethanol (11 mL) was added 28 v/v % aqueous ammonia solution (2.6 mL) with ice cooling, and the resulting mixture was stirred overnight at room temperature. The reaction mixture was neutralized with 2N hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water and brine sequentially and dried over anhydrous sodium sulfate. The residue was stirred for 30 minutes in isopropanol (20 mL) under heating and filtered to obtain a solid. The resulting solid was dried to give the title compound (1.37 g) having the following physical data.

TLC: Rf 0.47 (methylene chloride : methanol : acetic acid = 90 : 10 : 1).

Example 10: N-(2-cyano-3,4-dihydro-2H-1,4-benzoxazin-8-yl)-4-(4-phenylbutoxy)benzamide

To a solution of the compound prepared in Example 9 (1.11 g) in pyridine (10 mL) was added trifluoroacetic anhydride (1.06 ml) with ice cooling, and the mixture was stirred for 15 minutes, and futher stirred for 30 minutes at room temperature. The reaction mixture was poured into 2N hydrochloric acid and extracted with ethyl acetate. The organic layer was washed sequentially with water, saturated aqueous sodium bicarbonate solution and saturated brine, dried over anhydrous sodium sulfate and concentrated. To the residue were added tetrahydrofuran (5 ml) and ethanol (5 mL), and 1N aqueous potassium carbonate solution (2.5 mL) was further added thereto. The mixture was stirred for 15 minutes. After further addition of 1N aqueous potassium carbonate solution (2.5 mL), the mixture was stirred at room temperature for 15 minutes. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed sequentially with water and saturated brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by column chromatography on silica gel (n-hexane : ethyl acetate = 1 : 1) and then recrystallized from a mixed solvent of isopropanol (2 mL) and n-hexane (2 mL) to give the title compound (870 mg) having the following physical data.

TLC: Rf 0.52 (n-hexane : ethyl acetate = 2 : 3).

Example 11:

methyl

4-(2-cyano-8-((4-(4-phenylbutoxy)benzoyl)amino)-2,3-dihydro-4H-1,4-benzoxazin-4-yl)-4-oxo butanoate

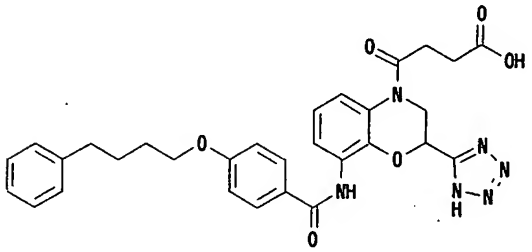
To a solution of the compound prepared in Example 10 (214 mg) in pyridime (2 mL) was added 3-(carbomethoxy)propionyl chloride (92 μL), and the mixture was stirred overnight at room temperature. Thereto was added another 3-(carbomethoxy)propionyl chloride (92 μL) and the resulting mixture was stirred for 4 hours. The reaction mixture was poured into 1N hydrochloric acid and extracted with ethyl acetate. The organic layer was washed sequentially

with water, saturated aqueous sodium bicarbonate solution and saturated brine, dried over anhydrous sodium sulfate and concentrated. The residue was recrystallized from a mixed solvent of ethyl acetate and n-hexane (1 : 1) to give the title compound (200 mg) having the following physical data.

TLC: Rf 0.37 (n-hexane : ethyl acetate = 2 : 3).

Example 12:

4-oxo-4-(8-((4-(4-phenylbutoxy)benzoyl)amino)-2-(1H-tetrazol-5-yl)-2,3-dihydro-4H-1,4-benzoxazin-4-yl)butanoic acid



To a solution of the compound prepared in Example 11 (196 mg) in N,N-dimethylformamide (2 mL) were added sodium azide (71 mg) and ammonium chloride (58 mg), and the mixture was stirred for 1 hour at 100°C. The reaction mixture was poured into 1N hydrochloric acid and the resulting mixture was extracted with ethyl acetate. The organic layer was washed sequentially with water and saturated brine, dried over anhydrous sodium sulfate and concentrated. The residue was dissolved in a mixture of tetrahydrofuran (1 mL) and methanol (1 mL), and thereto was added 1N aqueous solution of sodium hydroxide (1 mL) and the resulting mixture was stirred for 2 hours at room temperature. The reaction mixture was acidified with 2N hydrochloric acid and extracted with ethyl acetate. The organic layer was washed sequentially with water and saturated brine, dried over anhydrous sodium sulfate and concentrated. The residue was stirred in ethyl acetate (4 mL) for 30 minutes under heating, and the resulting solid was collected by filtration and it was dried to give the compound of the present invention (177 mg) having the following physical data.

TLC: Rf 0.40 (methylene chloride : methanol : acetic acid = 80 : 20 : 1);

^{1}H-NMR(CD_3CO_2D): δ 1.71-1.92, 2.58-2.81, 2.82-3.06 4.07, 4.42, 6.13, 6.96-7.30, 7.50, 7.84, 7.95.

Example 12(1) - Example 12(4)

The compounds of the present invention having the following physical data were prepared by using a corresponding hydroxynitrobenzoic acid instead of 2-hydroxy-3-nitrobenzoic acid, and using a corresponding acid chloride instead of 3-(carbomethoxy)propionyl chloride in the process of Example 1→Example 2→Example 3→Example 4→Example 5→Example 6→Example 9→Example 10→Example 11→Example 12.

Example 12(1):

5-oxo-5-(8-((4-(4-phenylbutoxy)benzoyl)amino)-2-(1H-tetrazol-5-yl)-2,3-dihydro-4H-1,4-benzoxazin-4-yl)pentanoic acid

TLC: Rf 0.44 (methylene chloride : methanol : acetic acid = 80 : 20 : 1);

^{1}H-NMR(DMSO-d_6): δ 1.72, 2.22, 2.63, 4.06, 4.22, 6.09, 6.97, 7.03, 7.22, 7.45, 7.68, 7.90, 9.40, 12.02.

Example 12(2):

6-oxo-6-(8-((4-(4-phenylbutoxy)benzoyl)amino)-2-(1H-tetrazol-5-yl)-2,3-dihydro-4H-1,4-benzoxazin-4-yl)hexanoic acid

TLC: Rf 0.50 (methylene chloride : methanol : acetic acid = 80 : 20 : 1);

^{1}H-NMR(DMSO-d_6): δ 1.49, 1.72, 2.20, 2.62, 4.06, 4.21, 6.09, 6.96, 7.04, 7.22, 7.47, 7.67, 7.90, 9.41, 11.99.

Example 12(3):

4-oxo-4-(6-((4-(4-phenylbutoxy)benzoyl)amino)-2-(1H-tetrazol-5-yl)-2,3-dihydro-4H-1,4-benzoxazin-4-yl)butanoic acid

TLC: Rf 0.36 (methylene chloride : methanol : acetic acid = 40 : 10 : 1);

^{1}H-NMR(CD_3CO_2D): δ 1.73-1.91, 2.58-2.84, 2.91-3.12, 3.99-4.29, 4.46-4.70, 5.88-6.01, 6.99, 7.05, 7.11-7 .34, 7.45-7.84, 7.86-8.17.

Example 12(4):

4-oxo-4-(7-((4-(4-phenylbutoxy)benzoyl)amino)-2-(1H-tetrazol-5-yl)-2,3-dihydro-4H-1,4-benzoxazin-4-yl)butanoic acid

TLC: Rf 0.39 (methylene chloride : methanol : acetic acid = 40 : 10 : 1);

^{1}H-NMR(CD_3CO_2D): δ 1.73-1.91, 2.58-2.86, 2.88-3.05, 3.97-4.38, 4.41-4.71, 5.91-6.07, 6.96-7.03, 7.10-7.59, 7.62-7.87, 7.90-7.97.

Example 13: 2-hydroxyphenyl benzoate

Sodium carbonate (63.6 g) was added to a solution of pyrocatechol (55 g) in water (230 mL), and to the resulting mixture was added dropwise benzoyl chloride (58 mL) over a period of 2 hours with vigorous stirring. The reaction mixture was stirred for 1 hour at room temperature. The reaction mixture was acidified carefully by dropwise addition of 2N hydrochloroic acid (350 mL) and then extracted with ethyl acetate. The organic layer was washed sequentially with water and saturated brine, dried over anhydrous sodium sulfate and concentrated. The residue was recrystallized from a mixed solvent of ethyl acetate (100 mL) and n-hexane (400 mL) to give the title compound (64.6 g) having the following physical data.

TLC: Rf 0.50 (n-hexane : ethyl acetate = 2 : 1).

Example 14: 2-hydroxy-3-nitrophenyl benzoate

To a suspension of the compound prepared in Example 13 (53.56 g) in acetic acid (500 mL)

was added dropwise concentrated nitric acid (61%, 18.7 mL) over a period of approximately 1 hour at 10°C. After 1 hour stirring, the reaction mixture was poured into ice water (1 L) and a precipitated solid was washed with water. The solid was recrystallized from isopropanol to give the title compound (19.6 g) having the following physical data.

TLC: Rf 0.68 (n-hexane : ethyl acetate = 2 : 1).

Example 15: 2-(benzyloxy)-3-nitrophenyl benzoate

The compound prepared in Example 14 (24.6 g) in N,N-dimethylformamide (95 mL) were added potassium carbonate (19.7 g) and benzyl bromide (12.4 mL), and the mixture was stirred overnight at room temperature. The reaction mixture was poured into water and the resulting mixture was extracted with ethyl acetate. The organic layer was washed with water and brine sequentially, dried over anhydrous sodium sulfate and concentrated. The residue was recrystallized from a mixture of ethyl acetate (50 mL) and n-hexane (200 mL) to give the title compound (29.4 g) having the following physical data.

TLC: Rf 0.47 (n-hexane : ethyl acetate = 4 : 1).

Example 16: 2-(benzyloxy)-3-nitrophenol

To a mixture of the compound prepared in Example 15 (27.9 g), tetrahydrofuran (100 mL) and ethanol (100 mL) was added 2N aqueous solution of sodium hydroxide (100 mL), and the mixture was stirred for 30 minutes at 50°C. The reaction mixture was ice-cooled and thereto was added 1N hydrochloric acid (120 mL), followed by concentration. The residue was purified by column chromatography on silica gel (n-hexane : ethyl acetate = 5 : 1) to give the title compound (19.6 g) having the following physical data.

TLC: Rf 0.40 (n-hexane : ethyl acetate = 2 : 1).

Example 17: 2-(benzyloxy)-1-(methoxymethoxy)-3-nitrobenzene

To a solution of the compound prepared in Example 16 (3.92 g) in methylene chloride (48 mL) were added N,N-diisopropylethylamine (4.18 mL) and chloromethyl methyl ether (1.46 mL) at 0°C, and the mixture was stirred for 1 hour at 25°C. The reaction mixture was concentrated, and water was added to the resulting residue and then the mixture was extracted with ethyl acetate. The organic layer was washed sequentially with 0.5N hydrochloric acid, water, saturated aqueous solution of sodium bicarbonate and brine, dried over anhydrous sodium sulfate and concentrated to give the title compound (4.63 g) having the following physical data.

TLC: Rf 0.58 (n-hexane : ethyl acetate = 2 : 1).

Example 18: 2-amino-6-(methoxymethoxy)phenol

To a mixture of the compound prepared in Example 17 (12.5 g), ethyl acetate (75 mL) and ethanol (75 mL) was added 10% palladium-carbon (314 mg), and the mixture was stirred for 5 hours under atmosphere of hydrogen. The catalyst was filtered off and the filtrate was

concentrated. The residue was recrystallized from a mixture of ethyl acetate and n-hexane to give the title compound (5.45 g) having the following physical data.

TLC: Rf 0.50(n-hexane : ethyl acetate = 1 : 1).

Example 19: ethyl 8-(methoxymethoxy)-3,4-dihydro-2H-1,4-benzoxazine-2-carboxylate

To a solution of the compound prepared in Example 18 (777 mg) in acetone (20 mL) were added ethyl 2,3-dibromopropionate (1.0 mL) and potassium carbonate (1.90 g) under atmoshophere of argon, and the mixture was stirred overnight at 50°C. After further addition of ethyl 2,3-dibromopropionate (1.0 mL) and potassium carbonate (1.90 g) under atmoshophere of argon, the mixture was stirred for 2 hours at 50°C. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed sequentially with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by column chromatography on silica gel (methylene chloride : ethyl acetate = 40 : 1) to give the title compound (416 mg) having the following physical data.

TLC: Rf 0.53 (methylene chloride : ethyl acetate = 10 : 1).

Example 20:

ethyl

8-(methoxymethoxy)-4-(4-methoxy-4-oxobutanoyl)-3,4-dihydro-2H-1,4-benzoxazine-2-carboxylate

To a solution of the compound prepared in Example 19 (416 mg) in pyridine (10 mL) was added 3-(carbomethoxy)propionyl chloride (288 μl), and the mixture was stirred for 1.5 hours at room temperature. The reaction mixture was diluted with water, and extracted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid, water, a saturated aqueous solution of sodium bicarbonate and saturated brine, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by column chromatography on silica gel (n-hexane : ethyl acetate = 3 : 2) to give the title compound (509 mg) having the following physical data.

TLC: Rf 0.38(n-hexane : ethyl acetate = 1 : 1).

Example 21:

ethyl 8-hydroxy-4-(4-methoxy-4-oxobutanoyl)-3,4-dihydro-2H-1,4-benzoxazine-2-carboxylate

To the compound prepared in Example 20 (509 mg) was added 4N hydrochloric acid in ethyl acetate (1.6 mL), and the mixture was stirred for 45 minutes at 0°C. The reaction mixture was concentrated and the residue was azeotroped with benzene. The residue was purified by column chromatography on silica gel (n-hexane : ethyl acetate = 1 : 1) to give the title compound (437 mg) having the following physical data.

TLC: Rf 0.32 (n-hexane : ethyl acetate = 1 : 1).

Example 22:

ethyl

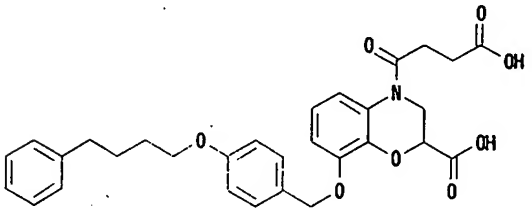
4-(4-methoxy-4-oxobutanoyl)-8-((4-(4-phenylbutoxy)benzyl)oxy)-3,4-dihydro-2H-1,4-benzoxazine-2-carboxylate

To a mixture of the compound prepared in Example 21 (430 mg), 1-(chloromethyl)-4-(4-phenylbutoxy)benzene (420 mg) and N,N-dimethylformamide (5 mL) was added potassium carbonate (263 mg), and the mixture was stirred for 3 hours at room temperature and for 5 hours at 50°C. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by column chromatography on silica gel (n-hexane : ethyl acetate = 2 : 1) to give the title compound (540 mg) having the following physical data.

TLC: Rf 0.42 (benzene : ethyl acetate = 4 : 1).

Example 23:

4-(3-carboxypropanoyl)-8-((4-(4-phenylbutoxy)benzyl)oxy)-3,4-dihydro-2H-1,4-benzoxazine-2-carboxylic acid



To a mixture of the compound prepared in Example 22 (193 mg), tetrahydrofuran (1 mL) and ethanol (1 mL) was added 2N aqueous sodium hydroxide solution (1 mL), and the mixture was stirred for 2 hours at room temperature and for 1 hour at 50°C. The reaction mixture was concentrated and the residue was diluted with water, acidified with 2N hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated. The resulting solid was recrystallized from a mixture of ethyl acetate, tetrahydrofuran and n-hexane to give the compound of the present invention (57 mg) having the following physical data.

TLC: Rf 0.44 (methylene chloride : methanol = 5 : 1);

^{1}H-NMR(DMSO-d_6): δ 1.71, 2.32-2.94, 3.67, 3.98, 4.37, 4.92-5.12, 6.74-6.96, 7.12-7.31, 7.35.

Example 24:

ethyl

4-(4-methoxy-4-oxobutyl)-8-((4-(4-phenylbutoxy)benzyl)oxy)-3,4-dihydro-2H-1,4-benzoxazine-2-carboxylate

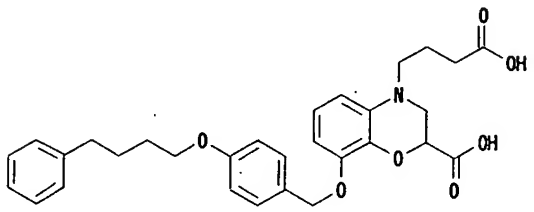
To a solution of the compound prepared in Example 22 (301 mg) in anhydrous tetrahydrofuran (3 mL) was added borane-dimethylsulfide complex (148 μL) in argon atmosphere with ice cooling, and the mixture was stirred for 45 hours at room temperature. To the reaction mixture

was added acetone, and the mixture was stirred for another 30 minutes. The reaction mixture was concentrated and to the resulting residue was added ethyl acetate. The organic layer was washed sequentially with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by column chromatography on silica gel (n-hexane : ethyl acetate = 3 : 1) to give the title compound (136 mg) having the following physical data.

TLC: Rf 0.51 (n-hexane : ethyl acetate = 1 : 1).

Example 25:

4-(3-carboxypropyl)-8-((4-(4-phenylbutoxy)benzyl)oxy)-3,4-dihydro-2H-1,4-benzoxazine-2-carboxylic acid



To a mixture of the compound prepared in Example 24 (134 mg), tetrahydrofuran (1 mL) and ethanol (1 mL) was added 2N aqueous sodium hydroxide solution (715 μL), and the mixture was stirred for 2 hours at room temperature. The reaction mixture was concentrated and the residue was diluted with water. The solution was acidified with 2N hydrochloric acid and extracted with ethyl acetate. The organic layer was washed sequentially with water and saturated brine, dried over anhydrous sodium sulfate and concentrated. The residue was recrystallized from a mixture of ethyl acetate, tetrahydrofuran and n-hexane to give the compound of the present invention (84 mg) having the following physical data.

TLC: Rf 0.64 (methylene chloride : methanol = 5 : 1);

^{1}H-NMR($CDCl_3$): δ 1.73-1.95, 2.37, 2.68, 3.07, 3.42, 3.52, 3.95, 4.94, 5.02, 5.08, 6.38, 6.73, 6.85, 7.14-7.37.

Example 25(1):

The compound of the present invention having the following physical data was prepared by using a corresponding acid chloride in stead of 3-(carbomethoxy)propionyl chloride in the process of Example 20→Example 21→Example 22→Example 24→Example 25.

Example 25(1):

4-(4-carboxybutyl)-8-((4-(4-phenylbutoxy)benzyl)oxy)-3,4-dihydro-2H-1,4-benzoxazine-2-carboxylic acid

TLC: Rf 0.43 (methylene chloride : methanol = 5 : 1);

^{1}H-NMR($CDCl_3$): δ 1.53-1.74, 1.75-1.85, 2.30-2.39, 2.68, 3.00, 3.34-3.60, 3.95, 4.97, 5.04, 5.10, 6.38, 6.72, 6.85, 7.14-7.22, 7.24-7.37.

Example 26: tert-butyl (3-amino-2-hydroxyphenyl)carbamate

To a solution of the compound prepared in Example 2 (2.93 g) in ethanol (20 mL) was added 10% palladium carbon (50 w/w %, hydroscopic, 400 mg) under atmosphere of argon, and the mixture was stirred for 5.5 hours under atmosphere of hydrogen. The catalyst was filtered off and the filtrate was concentrated to give the title compound having the following physical data.

TLC: Rf 0.32 (n-hexane : ethyl acetate = 3 :1).

Example 27:

ethyl 8-((tert-butoxycarbonyl)amino)-3,4-dihydro-2H-1,4-benzoxazine-2-carboxylate

The title compound having the following physical date (1.61 g) was obtained by substituting the compound prepared in Example 26 for the compound prepared in Example 18 in the process of Example 19.

TLC: Rf 0.24(n-hexane : ethyl acetate = 2 : 1).

Example 28:

4-(8-((tert-butoxycarbonyl)amino)-2-(ethoxycarbonyl)-2,3-dihydro-4H-1,4-benzoxazin-4-yl)butanoic acid

Under atmosphere of argon, to a solution of the compound prepared in Example 27 (100 mg), 4-oxobutanoic acid (15 w/w % aqueous solution, 422 mg) and acetic acid (45 mg) in ethanol was added 10% palladium-carbon (50 w/w %, hydroscopic, 10 mg), and the mixture was stirred for 30 minutes under atmosphere of hydrogen at room temperature. The catalyst was filtered off and the filtrate was concentrated. The residue was dissolved in a saturated aqueous solution of sodium bicarbonate and the resulting mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated to give the title compound (110 mg) having the following physical data.

TLC: Rf 0.34 (n-hexane : ethyl acetate = 1 : 2).

Example 29:

ethyl

8-((tert-butoxycarbonyl)amino)-4-(4-methoxy-4-oxobutyl)-3,4-dihydro-2H-1,4-benzoxazine-2-carboxylate

The compound prepared in Example 28 (110 mg) was dissolved in ethyl acetate (2 mL), and to the solution was added trimethylsilyldiazomethane (2M solution in hexane, 0.40 mL). The mixture was stirred for 1 hour at room temperature and concentrated. The residue was purified by column chromatography on silica gel (n-hexane : ethyl acetate = 85 : 15 → 80 : 20) to give the title compound (65 mg) having the following physical data.

TLC:Rf 0.28 (n-hexane : ethyl acetate = 3 : 1).

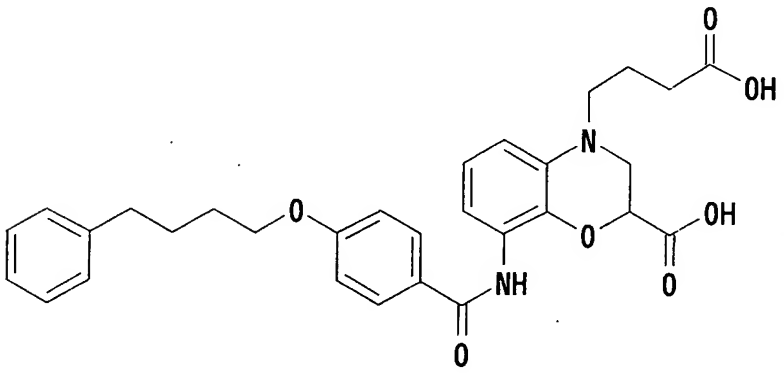
Example 30:

ethyl
4-(4-methoxy-4-oxobutyl)-8-((4-(4-phenylbutoxy)benzoyl)amino)-3,4-dihydro-2H-1,4-benzoxazine-2-carboxylate

The title compound (26 mg) having the following physical data was obtained by substituting the compound prepared in Example 29 (61 mg) for the compound prepared in Example 2 in the process of Example 3→Example 4.

TLC: Rf 0.26(n-hexane : ethyl acetate = 2 : 1).

Example 31:
4-(3-carboxypropyl)-8-((4-(4-phenylbutoxy)benzoyl)amino)-3,4-dihydro-2H-1,4-benzoxazine-2-carboxylic acid



The title compound (15 mg) having the following physical data was obtained by substituting the compound prepared in Example 30 (25 mg) for the compound prepared in Example 7 in the process of Example 8.

TLC: Rf 0.12 (methylene chloride : methanol = 9 : 1);

^{1}H-NMR(DMSO-d_6): δ 1.64-1.80, 2.14-2.34, 2.63, 3.08-3.38, 4.05, 4.49-4.56, 6.47, 6.68, 7.02, 7.13-7.31, 7.85, 9.07.

The effects of the compound of formula (I) of the present invention were illustrated by the following experiments, but the present invention is not limited to them.

Biological Example 1 : Effect on LTD_4-induced increase of intracellular calcium

Expression cells of $cysLT_2$ receptor (HEK293) were seeded in a 96-well plate each containing $1x10^5$cells. The cells were cultured for 24 hours in a 5% CO_2 at 37℃ using DMEM (Dulbecco's Modified Eagle Medium). The cells were incubated in 7.5μM Fura2-AM, 20 mM HEPES (2-[4-(2-hydroxyethyl)-1-piperazinyl]ethanesulfonic acid) and 2.5 mM probenecid for approximately 30 minutes at 37℃. The cells with uptake of Fura2-AM were once washed with assay buffer (Hank's buffer containing 20 mM HEPES) and intracellular calcium influx induced by LTD_4 was measured by FDSS2000 (Hamamatsu Photonics K.K.). The compound of the present invention was administered 180 seconds before LTD_4 stimulation,

and the reaction induced by 100 nM LTD_4 was measured in time course for 90 seconds. The effect of the compound of the present invention was evaluated by maximum fluorescence intensity, and 50% inhibitory concentration (IC_{50}) was calculated on each compound.

Biological Example 2: Effect on LTC_4-induced contraction in guinea pig trachea

Four Hartley male guinea pigs (Charles River Laboratories Japan, Inc.) per group were used in the present experiment. The guinea pigs were sacrificed by blood loss from carotid artery, and their tracheas were removed immediately. The tracheas were cut in a zigzag way with a razor to prepare a specimen with 3 mm width. The specimen was kept at 37°C and suspended in a 10 mL Magnus tube containing Tyrode solution (NaCl 137 mM, KCl 2.68 mM, $MgCl_2$ 1.05 mM, $CaCl_2$ 1.80 mM, $NaHCO_3$ 11.9 mM, NaH_2PO_4 0.417 mM and glucose 5.55 mM) aerated with mixed gas (95% O_2 + 5% CO_2) at 37℃. The tracheal specimen was given 1 G of tension and washed with Tyrode solution 3 times every 15 minutes. When the response being reached a steady state, the specimen was incubated in 45 mM serine-borate complex and 3 mM cysteine before LTC_4 stimulation. The contraction of trachea induced by LTC_4 was measured as the change of isometric tension by an isometric transducer. The compound of the present invention was administered 15 minutes before LTC_4 stimulation, and the time course of the tension induced by LTC_4 was observed. The rate of trachea contraction induced by LTC_4 was measured from the maximum response at the final concentration 1 mM of acetylcholine to calculate it on each comnpound. The antagonistic effect of the compound of the present invention against LT was determined by Schild plot analysis giving the pA_2 values.

It was revealed from the results that the compound of formula (I) significantly inhibited contraction in guinea pig trachea at more than 6 of pA_2 values.

Biological Example 3: Effect on OVA-induced bronchocontraction involved in endogenous LT in guinea pigs

Guinea pigs were actively sensitized by intraperitoneal administration of 1ml of saline containing 1mg ovalbumin (OVA) containing $5x10^9$ killed *Bordetella pertussis* cells. Two or three weeks after the sensitization, the guinea pigs were anesthetized with pentobarbital sodium (75 mg/kg, i.p.), and a polyethylene tube was inserted into the trachea which had been incised. For administration of the compound of the present invention and OVA, the jugular vein was cannulated. One side of the tracheal cannula was connected to a constant volume respirator and the animals were artificially ventilated with a contsant volume of 5 mL at a frequency of 70 strokes/min. Bronchocontraction was induced by intravenous administration of OVA, and airway resistance was measured by Konzett & Rössler method. In order to avoid the influence of cyclooxygenase metabolites and histamine, indomethacin (5 mg/kg/mL) and pyrilamine (1 mg/kg/mL) were intravenously administered 3 and 1 minute(s) before OVA challenge. Bronchocontraction was measured until the time of 20 minutes after OVA challenge, and

brochocontraction rate was calculated with time wherein the maximal insufflation pressure obtained by completely clamping off the trachea is set to 100 %.

It was revealed from the results that the compound of formula (I) suppresses bronchocontraction significantly, and is useful for the treatment of respiratory diseases, particularly of bronchial asthma.

[Formulation Example]

The formulations to be used in order to carry out the present invention are shown below.

Formulation Example 1

The following components were admixed by conventional techniques, thereby to give 10,000 tablects each containing 10 mg of active ingredient.

·4-(3-carboxypropanoyl)-8-((4-(4-phenylbutoxy)benzoyl)amino)-3,4-dihydro-2H-1,4-benzoxazine-2-carboxylic acid (100 g);

·carboxymethyl cellulose calcium (disintegrating agent) (20 g);

·magnesium stearate (lubricating agent) (10 g);

·microcrystalline cellulose (870 g).

[Industrial Applicability]

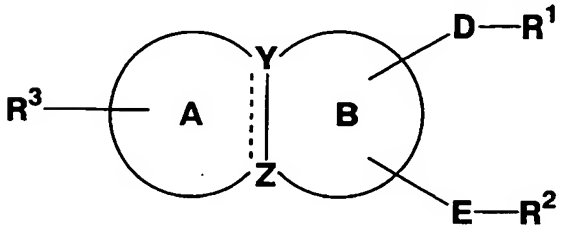
Since the compound of formula (I), a pharmaceutically acceptable salt thereof, a solvate thereof or a prodrug thereof antagonizes cysLT$_2$ receptor, it is useful as an inhibitor of airway contraction, an inhibitor of infiltration of inflammatory cells (e.g. eosinophils, neutrophils, lymphocytes, basophils, etc.), an inhibitor of mucus secretion or an inhibitor of increased airway hyperreactivity. And the compound of formula (I), , a salt thereof, a solvate thereof or a prodrug thereof is also useful for the prevention and/or treatment of those diseases with which cysLT$_2$ receptor is involved, e.g. respiratory diseases (e.g. bronchial asthma, chronic obstructive pulmonary diseases, lung emphysema, chronic bronchitis, pneumonia (e.g. interstitial pneumonitis, etc.), severe acute respiratory syndrome (SARS), acute respiratory distress syndrome (ARDS), allergic rhinitis, sinusitis (e.g. acute sinusitis, chronic sinusitis, etc.), etc., and as an expectorant or an antitussive agent. And the compound of formula (I) of the present invention, a pharmaceutically acceptable salt thereof, a solvate thereof or a prodrug thereof is also useful as an agent for the improvement of respiratory functions.

[Name of Document] Abstract

[Abstarct]

[Problem] Those agents for respiratory diseases showing higher efficacy than the LT receptor antagonists which are placed on the market have been hoped for.

[Means to solve] The present invention relates to a compound of formula (I)



(wherein all symbols have the same meanings as described hereinbefore). The compound antagonizes cysLT$_2$ and therefore, it is useful as an agent for the prevention and/or treatment of respiratory diseases such as bronchial asthma, bronchial asthma, chronic obstructive pulmonary disease, pneumonectasia, chronic bronchitis, pneumonia (e.g. interstitial pneumonitis etc.), severe acute respiratory syndrome (SARS), acute respiratory distress syndrome (ARDS), allergic rhinitis, sinusitis (e.g. acute sinusitis, chronic sinusitis, etc.), and the like, or as an expectorant or antitussives.